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## INFORMATION FOR AUTHORS

First page following cover

## EDITORIALS

- 23 **Heart failure management: 25 years of progress** Norman Sharpe  
24 **Molecule-to-Malady** The Editors

## ORIGINAL ARTICLES

- 25 **Growth and change in the prescribing of anti-depressants in New Zealand: 1993-1997**  
Evan Roberts, Pauline Norris  
27 **Regional variation in anti-depressant dispensings in New Zealand: 1993-1997**  
Evan Roberts, Pauline Norris  
30 **Non-invasive methods for measuring data quality in general practice** Barry Gribben,  
Gregor Coster, Mike Pringle, Jonathan Simon  
33 **Delays in the investigation of allegations of child sexual abuse in the Wellington city  
district 1995-1996: a retrospective study** Sarah Halsted, Dawn Elder

## CARDIOLOGY SPECIAL

- 36 **Clinical use of beta-blocker therapy in patients with heart failure: a practical guide**  
Robert N Doughty, A Mark Richards  
38 **Spontaneous intramural aortic haematoma** Alan P Whelan, Michael JA Williams  
41 **Treatment delays for patients with acute myocardial infarction within the Coromandel  
region of New Zealand** Christopher Nunn, Mathew Scott, John Lennane  
44 **Outcome following heart transplantation in Maori and Polynesian patients:  
a comparison with European New Zealanders** R D'Costa, PN Ruygrok, HA Coverdale,  
TM Agnew, HC Gibbs, D Reddy, DA Haydock, AR Kerr, RML Whitlock

## MOLECULE-TO-MALADY

- 47 **Turning off growth signals in tumours: a new approach to cancer chemotherapy**  
William A Denny

## NEWSLETTER

(pages 1-6)

# THE NEW ZEALAND MEDICAL JOURNAL



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**Title page** – the title should be brief without abbreviations. Authors' names, with only one first name and no degrees should be accompanied by position and workplace at the time of the study. Corresponding author details with phone, fax and email should be given, and the text word count noted.

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**References** – in the text use superscript numbers for each reference. Titles of journals are abbreviated according to the style used by Index Medicus for articles in journals the format is: Braatvedt GD. Outcome of managing impotence in clinical practice. NZ Med J 1999; 112: 272-4. For book chapters the format is: Marks P. Hypertension. In: Baker J, editor. Cardiovascular disease. 3rd ed. Oxford: Oxford University Press; 1998. p567-95. Note all authors

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## Addresses

**Editorial:** All editorial correspondence is sent to Professor Nicholls, c/o Department of Medicine, Christchurch Hospital, PO Box 4345 Christchurch, New Zealand. Telephone (03) 364 1116; Facsimile (03) 364 1115; email [barbara.griffin@chmeds.ac.nz](mailto:barbara.griffin@chmeds.ac.nz)

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## EDITORIALS

### Heart failure management: 25 years of progress

**Norman Sharpe, Professor, Division of Medicine, School of Medicine, University of Auckland, Auckland.**

In the late 1970's, the standard therapy for chronic congestive heart failure was digitalis and diuretics to improve heart pump function and relieve congestion. Vasodilator drugs were being studied at the time with the promise that 'unloading' the heart, which was suffering from high preload and afterload, might add benefit. One agent of particular interest, was captopril, the first orally active angiotensin converting enzyme (ACE) inhibitor for which haemodynamic improvement in heart failure was demonstrated. At the same time, investigators in Gothenburg, Sweden, reported remarkable improvement in cardiac performance and clinical status in a small case series of heart failure patients treated with the betablocker metoprolol. Over the subsequent two decades, ACE inhibitors and betablockers have been clinical 'probes' that have assisted reinterpretation of heart failure pathophysiology and description of the modern neurohormonal paradigm which extended and clarified earlier cardiorenal and haemodynamic concepts.

ACE inhibitors were rapidly introduced into standard heart failure treatment recommendations in the 1980's, although full uptake in practice took some years. In contrast, betablocker treatment remained 'contraindicated', despite emerging insight into neurohormonal mechanisms. A higher standard of proof was required for these agents and this has now been provided. The evidence is quite clear and consistent from a series of randomised controlled trials that betablockers can provide substantial long-term benefit for heart failure patients.<sup>1-4</sup> Current treatment guidelines should now include the recommendation that a betablocker of proven benefit (carvedilol, metoprolol or bisoprolol) be considered as part of the standard treatment regimen. Practical guidance for their clinical use is outlined in the accompanying paper in this issue of the Journal, which emphasises important aspects of patient selection and drug application.<sup>5</sup>

It is important to have a clear understanding of the nature and size of the benefits of treatment with betablockers. The primary benefits of treatment are improved long-term outcomes, reduced hospitalisation and mortality, rather than symptomatic improvement. This is certainly so for patients with chronic stable heart failure as in most of the clinical trials. The size of the benefit from betablockers is large. To put this into perspective, digoxin has a neutral effect on mortality, and ACE inhibitors, from an overview of all studies, appear to reduce mortality in chronic heart failure by about 25%.<sup>6</sup> Betablockers, when added to standard treatment including ACE inhibitors, reduce mortality by a further relative 35%. Patients with chronic heart failure as represented in recent trials, are a very high-risk population

with an annual mortality of 10-15%, comparable to many of the worst forms of cancer. The NNT (number needed to treat) to prevent a single death with betablockers during one year of treatment is about 25 patients for those with chronic stable heart failure of moderate severity,<sup>4</sup> and the NNT is as low as fifteen for more severe unstable patients. For 'cardiovascular comparison,' the NNT for long term betablocker treatment post myocardial infarction is approximately 90 and the NNT for lipid-lowering statin treatment in patients with coronary artery disease, is about 150. These different cardiovascular treatments in different patient groups are all very effective, reducing relative risk 20-30% or more over several years. The low NNT for betablockers in heart failure reflects unusual efficacy in patients with particularly high absolute risk. Since betablockers effectively reduce hospitalisation for heart failure patients, the treatment is highly cost effective.

As always, questions and limitations remain. Patients in clinical trials of heart failure treatment are not necessarily representative of patients in the community. Most trials have tended to select somewhat younger, predominantly male patients with little comorbidity and with ventricular systolic dysfunction. In the community, patients with heart failure are older, with genders represented more equally, comorbidity frequent and primary diastolic dysfunction with preserved systolic function being common. Accurate diagnosis of heart failure in these patients is often difficult and management is often empirical rather than evidence based. The potential for harm will always be greater outside of the carefully monitored clinical trial setting. In elderly patients, treatment aims and priorities may differ, with improved symptoms, comfort and mobility, rather than survival, generally being of primary importance.

Debate continues on with questions as to whether the benefits of betablockers in heart failure are a class effect and what are relevant mechanisms. Metoprolol and bisoprolol are beta<sub>1</sub> – selective, compared with carvedilol, which is relatively nonselective and has vasodilating and other ancillary properties. The benefits of these three agents are remarkably consistent. A large, ongoing study is comparing carvedilol and metoprolol directly. In contrast, another trial with bucindolol, which has a somewhat similar profile to carvedilol, recently showed no clear benefit. There is no justification for extrapolation of the benefit beyond the agents mentioned that have been reliably tested and proven in properly designed and powered clinical trials.

While it is agreed that the main mechanism mediating long term improvement appears to be blockade of noxious sympathetic overactivation and heart rate slowing, the properties of different betablockers vary widely and potential

mechanisms are complex and numerous. Effects on cardiac beta receptor regulation, for example, are quite different between agents with and without intrinsic sympathomimetic activity. One mechanism of benefit that is closely linked to neurohormonal blockade, and associated with improved long-term outcomes, is ventricular remodelling.<sup>7</sup> Both ACE inhibition and betablockade improve ventricular remodelling in heart failure. Ventricular remodelling is a reliable surrogate for long-term outcomes and itself is now considered a primary treatment target.<sup>8</sup>

Heart failure is a common condition that is costly in every aspect. Management, particularly in the community, is difficult. Accurate diagnosis is of primary importance requiring careful clinical assessment and, ideally, access to echocardiography. Measurement of blood natriuretic peptides may also be helpful in this regard. Current drug treatment is extremely effective in improving patients' symptoms and long-term outcomes. Betablockers should now be considered as part of

standard therapy and applied according to revised guidelines with considerable care.

**Correspondence.** Professor Norman Sharpe, Division of Medicine, School of Medicine, University of Auckland, Auckland. Email: n.sharpe@auckland.ac.nz

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## Molecule-to-Malady

Today's issue of the Journal contains the first of a new series, Molecule to Malady, highlighting advances in the biomedical sciences that stand to make a major impact on clinical medicine.

We have invited contributions from leading New Zealand biomedical researchers, working both in this country and overseas. We have asked them to convey what they see as exciting advances in their fields, in a readable format appropriate for our readership. As seems often the case, the busiest and most productive have found the time to contribute.

We hope you find the series of interest. Suggestions, comments and criticisms can be directed to Professor Christine Winterbourn, who has overseen this endeavour.

Our plan is to publish between four and six articles, intermittently throughout the year. The first is by Professor Bill Denny of the Auckland Cancer Society Research Centre, University of Auckland. Professor Denny is codirector of a longstanding and highly successful drug design team which has been responsible for producing five potential anticancer drugs that have entered clinical trial. One of these, amsacrine, has made it through to clinical use in cancer chemotherapy. This is an impressive achievement in view of the small proportion of experimental compounds that ever reach this point. Here he describes a new class of drug they are pursuing and its exciting prospects.

The Editors

Britain has reached a new medical frontier. That is a cause, not for the dismay with which some religious organisations greeted it last week, but for rejoicing. There is a prospect now of curing ancient, degenerative and chronic diseases that cause untold pain and misery to millions. Human cloning for medical research, an expert British committee believes, should be given the go-ahead. As with the genome project, the research will go to the heart of creation.

And there, for some religious groups, is the rub. The research will examine how life develops from one fertilised cell to a trillion, distributed across 200 different categories in every person. A vital part of it would involve making embryo clones, using the same techniques as with Dolly the sheep, but now for purely medical purposes. It would mean placing the nucleus from an adult cell into an egg stripped of its own nucleus. The egg would then subdivide and grow into an embryo. While it was still the size of a pinhead, containing 100 cells, stem cells would be extracted.

Cardinal Thomas Winning, chairman of the bioethics committee of the Catholic bishops of Great Britain and Ireland, said that obtaining stem cells from a human embryo was morally wrong and would "shock and disappoint many" because it involved the destruction of a human life. But Lord Winston, director of research at London's Hammersmith hospital, made the right response: "Most people, when the science and possibilities are explained, will regard this as a sensible and moral decision," he said.

Guardian Weekly August 24-30, 2000: 12.

During a recent photography shoot for a cosmetics advertisement on the Caribbean island of St Bartholomew, actress and model Liz Hurley was caught by paparazzi sunbathing topless – and sucking on a baby's pink dummy.

It emerged that the dummy was Ms Hurley's latest method for giving up the half a pack of Marlboro Lights she smokes each day. A spokeswoman for Ms Hurley explained that nicotine patches did not seem to work for her. The idea for the dummy, she said, came from Desmond Morris's book *Manwatching*, which "equated smoking with a baby's desire to be breast fed."

Mr Morris was pleased to hear that Ms Hurley had taken his advice: "Only someone like Liz, whom I've never met, could make something like a dummy look chic and trendy. As far as I know she's the only person to have taken up my idea to suck on a dummy to fight the urge to light up."

Ron Davis. *BMJ* 2000; 321: 319.



## Growth and change in the prescribing of anti-depressants in New Zealand: 1993-1997

Evan Roberts, *Research Assistant*; Pauline Norris, *Senior Research Fellow, Health Services Research Centre, Institute for Policy Studies, Victoria University of Wellington and Wellington School of Medicine, University of Otago, Wellington.*

### Abstract

**Aims.** To examine changes in the prescribing of anti-depressants in New Zealand from 1993-1997, in terms of expenditure, the number of dispensings and days of therapy supplied.

**Method.** Data on subsidised dispensings of anti-depressant drugs during 1993 to 1997 were obtained from PHARMAC and analysed using SAS.

**Results.** The overall size of the anti-depressant market increased considerably over the study period. Government

expenditure rose 2.25 times, and 1.65 times as many days of anti-depressant medication were supplied in 1997 as in 1993. Most of this was due to the growth in prescribing of newer anti-depressants, but the use of older drugs remained constant.

**Conclusions.** In common with other countries, the use of newer agents is contributing to increased overall use of anti-depressant medication and government expenditure in New Zealand. Use of older drugs has not diminished substantially.

NZ Med J 2001; 114: 25-7

The last decade saw considerable changes in treating depression. Until the late 1980s, treatment often included tricyclic anti-depressants and psychotherapy.<sup>1</sup> Since 1988, three major new anti-depressants have been introduced to New Zealand. These two selective serotonin reuptake inhibitors (SSRIs), fluoxetine (1988) and paroxetine (1992), and one new monoamine oxidase inhibitor (MAOI) moclobemide (1990) changed depression treatment options substantially. The newer drugs are more expensive than older medications and were heavily marketed, but their superiority over older drugs is controversial. Recent reviews have concluded that there are no significant differences in clinical- or cost- efficacy between SSRIs and tricyclic anti-depressants.<sup>2,3</sup> Controversy also remains about the acceptability of the new anti-depressants' side effect profile.

During the 1990s, there has been increased recognition of the public health and economic impact of depression.<sup>4</sup> This is attributable, in part, to the interest of manufacturers of newer treatments in supporting economic evaluations and cost of illness studies.<sup>5</sup> The presence of new treatment options, and increased public awareness of depression have expanded the market for anti-depressants.

Overseas research has found substantial growth in anti-depressant prescribing and expenditure. In Ontario, anti-depressant expenditure for elderly residents increased 120% between 1990 and 1995, while the population receiving anti-depressants grew only 35%.<sup>3</sup> Donoghue et al found that anti-depressant prescriptions increased 30% between 1993 and 1995 in a group of general practices in the United Kingdom.<sup>6</sup> There is some evidence that growth in anti-depressant prescribing is composed of increased prescribing of newer drugs, while prescribing of older medications remains almost constant. At a population level, new drugs are not necessarily replacing older drugs, but are being used in addition.<sup>7,8</sup>

This paper examined changes in anti-depressant prescribing in New Zealand from 1993 to 1997. Firstly, we describe the changing level of expenditure, dispensings and number of days dispensed of all anti-depressant medication. We then examine the changing composition of the anti-depressant market, between new and old drugs. We addressed these questions using Health Benefits Limited (HBL) data on claims for prescriptions dispensed by New Zealand pharmacies. Overseas studies have often used sub-

national and unrepresentative databases such as general practice networks, Health Maintenance Organisation enrollees, municipalities, or samples of ambulatory care encounters.<sup>6,9-13</sup> An advantage of HBL data is its nearly complete population coverage for New Zealand. Data for the North Health region may be incomplete since, during the mid-1990s, they maintained their own database of dispensings which was added retrospectively to the HBL data.

### Methods

PHARMAC supplied HBL data from their data warehouse on subsidised dispensings of anti-depressants (3.9 million dispensings). Dispensings by community or hospital pharmacies were included, but not in-patient medication use. Dispensings do not represent prescriptions, since one prescription can result in several dispensings. The records cannot be linked to particular patients, so it was not possible to determine whether any two prescriptions were for the same person or different people. Therefore, we could not calculate how many people received anti-depressants, or how much medication each received.

The data included all prescriptions which received some government subsidy. Whether a pharmaceutical is subsidised depends on the drug price, size of the prescription, and entitlement status of the patient. Because a small prescription of cheap medicine to a person without a community service card may not have a subsidy, the database may exclude some dispensings of small quantities of cheaper anti-depressants. As the database was generated from payment of claims for dispensing, most fields had little missing data. In particular, fields required for calculating pharmacy reimbursements were almost always completed. The dataset were analysed using SAS.<sup>14</sup>

All expenditure figures reported are government expenditure adjusted to 1997 prices using the Consumer Price Index (CPI).<sup>15</sup> Should anti-depressant prices change at a different rate from general prices, CPI adjustment would give an inaccurate picture of the real volume of anti-depressants purchased.<sup>16</sup> Adjustment by the CPI indicates the value of non-anti-depressant commodities relinquished to purchase anti-depressants.<sup>17</sup> Between 1993 and 1997, cumulative growth in the CPI was 9.6%, while PHARMAC's pharmaceutical price index declined 14%. Thus, readers should not interrupt expenditure figures as a 'metric' of the real volume of anti-depressant dispensing.

### Results

The anti-depressant market grew significantly from 1993 to 1997. Total real cost to the government of anti-depressants doubled from \$26.4 million in 1993 to \$60.0 million in 1997 (Table 1). Length of supply rose from a total of 23.3 million days in 1993 to 38.5 million days in 1997 (Table 2). This is equivalent to an increase from

63 795 people taking anti-depressants continuously for a year in 1993 to 105 471 in 1997.

**Table 1. Government expenditure on anti-depressants: 1993-1997.**

Type of Antidepressant	Government expenditure (\$000)				
	1993	1994	1995	1996	1997
Tricyclic	8737	8178	8159	7908	8313
SSRI	11 666	20 566	26 893	32 423	44 661
Reversible MAOI	4825	4661	5022	5647	6322
Tetracyclic	671	515	458	373	339
MAOI	493	446	447	411	407
<b>Total</b>	<b>26 381</b>	<b>34 374</b>	<b>40 983</b>	<b>46 761</b>	<b>60 042</b>

SSRI = selective serotonin reuptake inhibitors. MAOI = monoamine oxidase inhibitors.

**Table 2. Days supplied of anti-depressants: 1993-1997.**

Type of Antidepressant	Days supplied (000)				
	1993	1994	1995	1996	1997
Tricyclic	18 407	18 574	19 227	18 457	20 875
SSRI	2970	6146	8306	10 067	15 465
Reversible MAOI	1313	1291	1349	1504	1763
Tetracyclic	346	283	249	198	194
MAOI	249	225	219	189	200
<b>Total</b>	<b>23 285</b>	<b>26 519</b>	<b>29 350</b>	<b>30 415</b>	<b>38 497</b>

SSRI = selective serotonin reuptake inhibitors. MAOI = monoamine oxidase inhibitors.

Between 1993 and 1995, the increase in expenditure was due both to an increase in the number of dispensings and an increase in the average real cost per dispensing. The number of dispensings rose steadily from 473 202 in 1993 to 598 246 in 1995 (Table 3). An average dispensing in 1993 cost the government \$51.29, rising to \$68.51 in 1995. Introduction of monthly dispensing in May 1996 artificially increased the number of dispensings and decreased average cost per dispensing. Because of this, in 1996, the number of dispensings jumped to 932 544, and rose to 1 350 319 in 1997.

**Table 3. Dispensings of anti-depressants: 1993-1997.**

Type of Antidepressant	Dispensings of anti-depressants				
	1993	1994	1995	1996	1997
Tricyclic	363 239	360 399	381 022	551 488	732 656
SSRI	67 150	133 156	177 311	321 336	540 494
Reversible MAOI	31 753	29 428	31 352	48 854	63 942
Tetracyclic	6346	5095	4308	5162	5976
MAOI	4714	3918	4253	5702	7240
<b>Total</b>	<b>473 202</b>	<b>531 996</b>	<b>598 246</b>	<b>932 544</b>	<b>1 350 319</b>

SSRI = selective serotonin reuptake inhibitors. MAOI = monoamine oxidase inhibitors.

Despite SSRIs' growing popularity, tricyclics continued to account for a large proportion of anti-depressant dispensings. In 1993, three tricyclics – amitriptyline, doxepin and dothiepin – were the most dispensed anti-depressants, followed by fluoxetine (an SSRI). Since 1994, fluoxetine has been the most dispensed anti-depressant, with the three tricyclics still being frequently dispensed. Since 1996, another SSRI, paroxetine, has been the third most dispensed anti-depressant. Tetracyclics and older MAOIs formed a small and declining proportion of dispensings (2.3% in 1993; 1% in 1997).

**Prescribing of newer and older anti-depressants.** Choices for anti-depressant drug therapy changed

substantially with the introduction of fluoxetine in 1988, moclobemide in 1990, and paroxetine in 1992. A third SSRI, sertraline, has become available but is subsidised in exceptional circumstances only. Soon after their introduction to the market in 1993, the new anti-depressants comprised 20.9% of the dispensings, yet they already claimed 62.5% of government expenditure on anti-depressants.

New drugs comprised an increasing percentage of dispensings (from 20.9% in 1993 to 44.8% in 1997), expenditure (from 62.5% in 1993 to 84.9% in 1997) and total days supplied (from 18.4% in 1993 to 44.8% in 1997). New anti-depressants' importance in the market place was most evident when measured by days supplied. By 1997, new anti-depressants accounted for 2.43 times as much of the total days of anti-depressant therapy supplied, 2.14 times as many dispensings, and 1.36 times as much of government expenditure as they did in 1993. Thus, the relative price of a day of new anti-depressant drug therapy declined between 1993 and 1997. Some of this relative price reduction is attributable to PHARMAC's contracting arrangement for fluoxetine since 1996. PHARMAC placed a cap on total subsidy payable in a single year. When expenditure exceeded the cap, the manufacturer (Eli Lilly) rebates the difference to PHARMAC.<sup>18</sup> The contract allowed general practitioners (GPs) to prescribe fluoxetine without a specialist's recommendation from 1 September 1996. Even prior to this change, non-specialist practitioners wrote the majority of fluoxetine prescriptions dispensed. In 1993, 79% of fluoxetine dispensings were made by non-specialists, growing to 87% of dispensings in 1997.

## Discussion

As also occurred internationally, New Zealand's consumption of anti-depressants grew substantially during the mid-1990s.<sup>7,8</sup> At a population level, the dispensing of older anti-depressants remained roughly constant, while consumption of newer anti-depressants has grown substantially. Government expenditure on new anti-depressants grew 3.1 times between 1993 and 1997 but growth was most dramatic for SSRI expenditure (3.8 fold). Hence, the growth in total government expenditure on anti-depressants can be attributed both to volume growth and to changes in composition; more anti-depressants are being dispensed and a growing proportion of anti-depressant consumption is of the more expensive newer drugs.

The growing rate of prescribing of anti-depressants in New Zealand could be due to several factors. The prevalence of depression could be increasing, patients could be presenting to their GPs with depression more often, or doctors could be identifying more patients as having a depressive disorder. Doctors could also be moving away from non-drug treatments for depression and prescribing more anti-depressants than in the past, or they may be prescribing anti-depressants for patients they had previously prescribed other drugs such as anxiolytics. Patients may be responding to increased marketing and discussion of anti-depressant medication and asking their doctors for these either directly or indirectly. Anti-depressant drugs are also being indicated for the treatment of conditions such as eating disorders. These explanations are not, of course, mutually exclusive. It is possible that some of these factors might have led to an increase in anti-depressant prescribing, even without the introduction of newer drugs since 1988. The lack of patient identifiers and diagnostic information in our data means that other sources are required to answer important questions about the efficacy and effectiveness (including cost-effectiveness) of depression treatment. Dispensing data alone

cannot identify whether the growth in anti-depressant consumption was beneficial overall, or for individuals.

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**Correspondence.** Evan Roberts, Department of History, University of Minnesota, Social Sciences, 267 19th Avenue South, Minneapolis, Minnesota 55455, USA. email: eroberts@hist.umn.edu

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## Regional variation in anti-depressant dispensings in New Zealand: 1993-1997

**Evan Roberts, Research Assistant; Pauline Norris, Senior Research Fellow, Health Services Research Centre, Institute for Policy Studies, Victoria University of Wellington and Wellington School of Medicine, University of Otago, Wellington.**

### Abstract

**Aims.** To examine regional differences in the prescribing of anti-depressants in New Zealand from 1993 to 1997, and to examine the composition and dynamics of these differences.

**Methods.** Data on every subsidised dispensing of anti-depressant drugs 1993 to 1997 were obtained from PHARMAC and analysed using SAS. Each dispensing was allocated to a regional council area on the basis of the location of the dispensing pharmacy.

*NZ Med J* 2001; 114; 27-30

**Results.** Prescribing of anti-depressants increased with time in all regions. However, there was substantial regional variation in prescribing rates per-capita, the highest being 2.28 to 2.49 times the lowest in every year. Regions also varied substantially in the mix of newer and older drugs used, although newer drugs became increasingly important in every region.

**Conclusions.** Regional differences in anti-depressant prescribing are large. Further research with different data sources is required to explore the reasons for this variation.

In a companion paper, we considered changes in anti-depressant prescribing in New Zealand between 1993 and 1997, examining days of anti-depressant therapy supplied, government expenditure and dispensings.<sup>1</sup> Growth in anti-depressant prescribing came from sustained growth in prescribing newer drugs, with constant use of older drugs. The previous paper emphasised changes over time. The present paper takes a cross-sectional approach, analysing regional differences in prescribing.

Internationally, there is evidence of variation in the rate of treatment between countries, between regions within countries, and between practitioners within regions.<sup>2-4</sup> Studies of prescribing variation are rare. Davis et al analysed CoMedCa data, and found practitioner identity significantly predicted prescribing behaviour.<sup>5</sup> Norris et al examined regional variation of prescribing of new antidepressants (fluoxetine, paroxetine and moclobemide) in New Zealand between October 1993 and March 1994.<sup>6</sup> They found high regional variation in dispensing of fluoxetine. Fluoxetine capsules prescribed per-capita in Canterbury were more than double the level in Waikato, which had the next highest level. Using a logarithmic decomposition, the nature of this variation was explored. Dispensings per-capita explained 89% of variance in dispensed capsules per-capita. Variation in prescriptions per person was thus more important than variation in prescription size. Another decomposition of the

variance showed that per-capita doctor supply explained 12% of the variance in capsules per population.

This paper examines regional variation in prescribing of all anti-depressants from 1993 to 1997. We consider whether there was any inter-regional variation over this period, and explore the composition of variation found.

### Methods

We obtained Health Benefits Limited (HBL) data on anti-depressant dispensings between 1993 and 1997, as discussed in our previous paper.<sup>1</sup>

Dispensings were mapped to geographical areas using the location of the dispensing pharmacy. Previous work by Norris et al<sup>6</sup> used doctors' locations. Pharmacy location was used as a proxy for the doctor's location, because pharmacy location data were more complete (between 1993 and 1997, 30.7% and 32.6% of prescribers were unable to be mapped to a region).

Norris et al used Area Health Board regions, which have no current administrative significance.<sup>6</sup> We used regional councils as our geographical areas, because there were a moderate number (sixteen) of them, and they were large enough to reduce problems from prescriptions being dispensed and prescribed in different areas. Regional council boundaries were stable, facilitating comparison between years. Population counts for regional councils were obtained from Supermap 3.0 for the census years 1991 and 1996.<sup>7</sup> We assumed there was linear inter-censal growth in population. Population estimates for 1997 were obtained from Statistics New Zealand. For each year we calculated, using SAS, for each regional council area, the number of anti-depressant dispensings per 1000 people, cost to the government per person, and days of anti-depressant drug therapy supplied per 1000 people.<sup>8</sup>



## Results

Nationwide, the level of anti-depressant prescribing, and the proportion of prescribing for newer drugs, rose substantially from 1993-1997,<sup>1</sup> a trend largely repeated within regions. Per-capita expenditure rose each year in every region (except in Gisborne where it fell 1994-5), the number of dispensings per 1000 people rose every year in every region, and the number of days supplied per 1000 people rose every year in every region (except for falls in Canterbury, Marlborough, Otago and Southland 1995-6 and Gisborne 1994-6). Despite similar growth rates, there was variation in anti-depressant dispensing levels after adjusting for population size.

Every year, Canterbury had the highest rate of anti-depressant dispensings per-capita, around 2.3 times higher than the rate in the lowest area: Northland (1993-5) and Gisborne (1996 and 7; Table 1). A similar pattern held for government expenditure and days supplied. Canterbury was always the highest region, with a rate of government expenditure between four and five times the lowest rate (Northland, Hawkes Bay or Gisborne; Table 2 and 3). Canterbury's per-capita rate of days supplied was over twice as high as the lowest rate (Northland or Gisborne; Table 4).

A measure of inter-regional variability is the population weighted coefficient of variation (CVW), which standardises variance by dividing it by the mean. Like the ratio of the highest-to-lowest levels, the CVW tended to be consistent across time for all three measures. The CVW was higher for per-capita government expenditure than for items or days supplied per 1000 people – a relationship that was stable over the period studied. Inter-regional variation was greater for expenditure than for days supplied or dispensings. In part, the CVW was higher for expenditure because regions with greater per-capita dispensings tended to have a higher ratio of newer to total drugs used.

Regions varied in the type of anti-depressants prescribed. Norris et al found that in 1993/94, Canterbury had the highest per capita rate of fluoxetine prescribing, and Southland the lowest.<sup>6</sup> We found that in 1993, the ratio of days supplied for older to newer drugs varied between 15.5 (Southland) and 3.6 (Canterbury). That is, for every day of newer anti-depressant medication supplied in Southland, 16 days were supplied of older anti-depressant medication. In the next year, the ratio of old-to-new days in Southland dropped to 7.6. This might partly reflect the smaller population of both prescribers and consumers in Southland. Canterbury always had the lowest ratio of old-to-new days supplied.

Over the period to 1997, there was substantial convergence between the regions in the composition (older/newer) of anti-depressant dispensings. In 1997, the ratio of older: newer days supplied varied between 2.3 (Gisborne) and 0.9 (Canterbury). Thus, by 1997, more days of newer than older anti-depressant medication were supplied in Canterbury. The same trend was evident for dispensings and government expenditure. Newer antidepressants became increasingly important in every region. Regions have become more alike than in 1993, shortly after the introduction of newer anti-depressants. Nevertheless, prescribing rates of both older and newer medications continued to vary between regions (Table 4).

The changing nature of regional variation was explored by decomposing the variance in days supplied and government expenditure. Causal analysis of regional variation was not possible with this dataset. Variation in expenditure per-capita could be due to a high number of dispensings or dispensings for expensive anti-depressants. Expenditure per-capita can be expressed as:  $\text{expenditure/population} = \text{dispensings/population} \times \text{expenditure/dispensings}$ .

Because  $\text{Var}(\ln(x.y)) = \text{Var}(\ln(x)) + 2\text{Cov}(\ln(x), \ln(y))$ , proportions of variance in the natural logarithm of expenditure per-capita can be attributed to the variances of the two components, and their covariance. This identity was calculated separately for all years from 1993-1997. Initially, the major contributor to variation in per-capita expenditure was variance in the average cost per dispensing. In 1993, this composed more than half the variance in per-capita expenditure, consistent with evidence above of regional convergence in the proportions of old and new medications dispensed. Covariance between the two terms has also grown, indicating that where there is higher prescribing per-capita, prescriptions are costlier on average.

Similarly, the days supplied per-capita could be due to the number of dispensings or to the length of dispensings. Days supplied per-capita can be expressed as:  $\text{days supplied/population} = \text{days supplied/dispensings} \times \text{dispensings/population}$ .

Per-capita dispensings over-explain variation in per-capita days supplied. In every year between 1993 and 1997, variation in per-capita dispensings accounted for more than 100% of the variance in per-capita days supplied, though this dropped over time (Table 6). Variation in average length of dispensing accounted for a small and diminishing percentage of variance in days supplied. The two terms 'over-explain' the variation found because per-capita dispensings and average length of dispensings are inversely related. On average, in regions where more dispensings were made, dispensings were shorter. This relationship became less significant over time and is partly attributable to monthly dispensing, as the maximum pharmacies can dispense is a month's supply.

## Discussion

The national trend of a substantial growth in anti-depressant prescribing between 1993 and 1997<sup>1</sup> was evident in all regions. Despite similarity in the pattern of growth, there was regional variation in prescribing levels. Using any of our three measures (dispensings, expenditure or days supplied), there was high inter-regional variation.

Norris et al found high rates of prescribing of new anti-depressants in Canterbury, but could not interpret this without information about overall prescribing rates.<sup>6</sup> We found on three different measures that anti-depressant prescribing rates in Canterbury were consistently high. Additionally, regions with higher dispensing rates per-capita tended to have higher ratios of new:total drugs dispensed. Canterbury had the highest level of new drugs prescribed as a proportion of the total. By 1997, more days of new drugs were prescribed than days of old drugs, putting the previous results in context. Norris et al thought the high use of new anti-depressants in Canterbury might be because Canterbury doctors used new drugs, when doctors elsewhere used older drugs. This paper shows that high prescribing of new drugs coincides with high use of anti-depressants in general, combined with greater use of newer therapies. This narrows down the range of explanations. It does not provide evidence on the prevalence or severity of depression in the regions. This may be higher in some regions, or it may be that prescribers in some regions are more sensitive to the possible existence of depression in their patients, or that they are more likely to use medication to treat depression. Because dispensing data also provide no information on variation in treatment outcomes between regions, it is not possible to assess where the level of anti-depressant prescribing is most appropriate to the prevalence and severity of depression.

There was variation among regions in use of new drugs. In 1993, there was substantial divergence in ratios of old:new anti-



**Table 1. Regional variation in dispensings per 1000 people.**

Year	1993	1994	1995	1996	1997
New Zealand rate	138.1	153.2	170.2	262.2	374.5
Highest rate (regional council)	221.8 (Canterbury)	249.6 (Canterbury)	269.8 (Canterbury)	387.7 (Canterbury)	545.6 (Canterbury)
Lowest rate (regional council)	95.9 (Northland)	100.2 (Northland)	114.3 (Northland)	169.5 (Gisborne)	236.8 (Gisborne)
Extremal quotient	2.31	2.49	2.36	2.28	2.30
Population weighted coefficient of variation	127.35	130.23	124.15	104.68	107.85

**Table 2. Regional variation in government expenditure per person.**

Year	1993	1994	1995	1996	1997
New Zealand rate	\$7.75	\$9.94	\$11.71	\$13.19	\$17.06
Highest rate (regional council)	\$16.38 (Canterbury)	\$20.64 (Canterbury)	\$23.48 (Canterbury)	\$25.35 (Canterbury)	\$29.50 (Canterbury)
Lowest rate (regional council)	\$3.70 (Northland)	\$4.41 (Northland)	\$5.78 (Hawkes Bay)	\$6.00 (Gisborne)	\$7.09 (Gisborne)
Extremal quotient	4.42	4.67	4.06	4.22	4.15
Population weighted coefficient of variation	224.43	217.90	203.25	184.63	161.06

**Table 3. Regional variation in days supplied per 1000 people.**

Year	1993	1994	1995	1996	1997
New Zealand rate	6790.4	7635.0	8350.6	8548.3	10 679.8
Highest rate (regional council)	10 164.1 (Canterbury)	11 834.6 (Canterbury)	12 807.7 (Canterbury)	12 524.3 (Canterbury)	15 525.3 (Canterbury)
Lowest rate (regional council)	4712.4 (Northland)	5142.0 (Northland)	5643.4 (Northland)	6075.5 (Gisborne)	7366.3 (Gisborne)
Extremal quotient	2.31	2.30	2.27	2.06	2.10
Population weighted coefficient of variation	107.82	116.76	116.55	103.16	106.47

**Table 4. Measures of prescribing of anti-depressants in regional council areas.**

Regional Council	Per-Capita Government Cost of Anti-depressants					Dispensings Per 1000 People					Days Supplied Per 1000 People				
	1993	1994	1995	1996	1997	1993	1994	1995	1996	1997	1993	1994	1995	1996	1997
Auckland	\$5.59	\$7.39	\$8.54	\$10.09	\$13.00	118	131	145	219	301	5773	6457	6990	7117	8629
Bay of Plenty	\$8.90	\$11.13	\$12.00	\$12.66	\$15.15	121	139	150	252	360	6742	7812	8374	8638	10 467
Canterbury	\$15.07	\$19.17	\$22.09	\$24.80	\$29.50	222	250	270	388	546	10 164	11 835	12 808	12 524	15 525
Gisborne	\$6.06	\$7.21	\$5.86	\$5.87	\$7.09	103	110	116	170	237	6126	6676	6603	6076	7366
Hawkes Bay	\$3.72	\$4.76	\$5.44	\$6.74	\$9.46	119	122	138	219	306	5616	5895	6257	6769	8357
Manawatu-Wanganui	\$5.89	\$8.80	\$10.53	\$12.20	\$16.85	122	149	160	256	379	5966	7134	7865	8230	10 679
Marlborough	\$5.49	\$9.30	\$11.36	\$13.67	\$18.82	163	184	210	286	429	9034	10 778	12 030	10 769	12 879
Nelson	\$4.71	\$7.74	\$11.99	\$15.25	\$17.58	148	172	208	307	419	7000	8062	9562	9821	11 912
Northland	\$3.40	\$4.11	\$5.53	\$10.31	\$15.71	96	100	114	219	330	4712	5142	5643	6897	9428
Otago	\$8.60	\$10.30	\$12.67	\$14.07	\$18.16	182	191	207	298	429	8545	9251	9978	9692	12 250
Southland	\$3.74	\$4.90	\$9.70	\$11.30	\$13.30	122	132	176	256	342	6183	6787	8540	8489	9787
Taranaki	\$5.46	\$6.71	\$9.56	\$12.65	\$17.11	156	166	195	311	469	7165	7716	8970	10 037	13 460
Tasman	\$3.79	\$5.26	\$7.19	\$9.44	\$12.53	112	121	134	201	294	6005	6294	6802	7075	8951
Waikato	\$6.91	\$9.06	\$10.53	\$11.58	\$15.45	116	133	153	240	351	6212	7111	7858	7973	10 010
Wellington	\$5.84	\$7.26	\$9.58	\$12.26	\$17.74	135	144	160	273	412	6873	7322	8079	8768	11 445
West Coast	\$6.85	\$9.62	\$10.92	\$12.16	\$16.27	137	162	181	253	372	5736	7392	7906	8408	11 528

**Table 5. Decomposition of regional variation in expenditure per person.**

Variable	Percentage of variance explained in year				
	1993	1994	1995	1996	1997
Dispensings per person	32.0	36.1	42.9	37.3	42.7
Expenditure per dispensing	56.6	40.0	27.1	24.6	21.8
Covariance	11.4	23.9	30.0	38.1	35.5

**Table 6. Decomposition of regional variation in days per person.**

Variable	Percentage of variance explained in year				
	1993	1994	1995	1996	1997
Dispensings per person	123.8	117.2	109.7	106.9	110.4
Days per dispensing	20.7	15.7	12.9	7.3	3.7
Covariance	-44.5	-32.9	-22.6	-14.2	-14.1

depressants. Some regions, such as Canterbury and the Bay of Plenty, used new anti-depressants quite frequently. Elsewhere, in Southland and Taranaki, new drugs were less widely dispensed. Over the next four years, the proportion of new drugs used converged between regions. At the beginning of the period, per-capita expenditure varied mostly because of this difference in the use of new drugs. By 1997, the difference had narrowed, and per-capita expenditure now varied mostly because of variation in dispensings per-capita. In 1997, expenditure per-capita on anti-depressants varied more than

four-fold. This was because doctors in some regions prescribed more and more expensive anti-depressants than doctors in other regions. These two trends exaggerated regional differences, rather than nullified them.

Although regional variation may seem substantial, it is evident (Table 4) that days supplied per 1000 people in Northland (a low use region) in 1997 were nearly as high as the days supplied in Canterbury (a high use region) in 1993, providing further evidence of regional convergence over time. It is possible that over time, the inter-regional differences will narrow further as

regions with low use of anti-depressants catch-up with regions where use is currently high.

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**Correspondence.** Evan Roberts, Department of History, University of Minnesota, Social Sciences, 267 19th Avenue South, Minneapolis, Minnesota 55455, USA. email: eroberts@hist.umn.edu

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## Non-invasive methods for measuring data quality in general practice

**Barry Gribben, Director RNZCGP Research Unit; Gregor Coster, Professor of General Practice, Department of General Practice and Primary Health Care, University of Auckland; Mike Pringle, Professor of General Practice, Department of General Practice, University of Nottingham, UK; Jonathan Simon, Medical Director, FirstHealth, Auckland.**

### Abstract

**Aim.** To develop non-invasive methods of measuring the quality of data recorded in general practice.

**Methods.** Laboratory and pharmaceutical claims data from fourteen practices (44 doctors) from the FirstHealth network of general practices were examined to determine the extent to which valid minimum bounds on expected rates of diagnosis coding could be established. These were compared with recorded rates in patient notes to measure completeness of diagnosis recording. Data completeness was measured for demographic data and a marker for the accuracy of gender coding was developed from diagnosis data.

**Results.** Minimum rates of diagnosis could be established for asthma, diabetes (NIDDM and IDDM), ischaemic heart disease, hypothyroidism, bipolar affective disorder

and Parkinson's disease. Minimum bounds for the number of patients requiring monitoring of warfarin and digoxin levels were also established. These expected minimum rates were combined with measures of completeness of age, gender, ethnicity and smoking data, and a gender coding accuracy measure, to produce a set of fourteen data quality indicators. Pass/fail thresholds on each indicator were set and each of the fourteen practices was scored on the number of passes they achieved. The scores ranged from three to nine out of fourteen passes.

**Conclusions.** Non-invasive data quality measures may be useful in providing feedback to general practitioners as part of a data quality improvement cycle. The sensitivity of this method will decline as data quality improves.

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Over the past decade, the amount of information collected in general practice (GP) has increased significantly. Across New Zealand, at least 85% of GPs now use computers.<sup>1</sup> Most often, computers are used for accounts and the maintenance of age/sex registers,<sup>2</sup> but increasingly, doctors are using practice management systems for clinical notes, prescribing and laboratory test ordering, as well as practice administration, and many doctors routinely code diagnoses using Read codes. Since this information is used for an increasing range of purposes, from the claiming of subsidies to disease surveillance, the quality of the data recorded by GPs will come under increasing scrutiny. Internationally, there is widespread interest in the introduction of information technology in primary care and the NHS Executive in the UK is funding a major programme to support the collection and analysis of primary care data, led by one of the authors (MP).

In November 1998, the RNZCGP Research Unit in the Department of General Practice and Primary Health Care at the University of Auckland was contracted by FirstHealth to develop methods for measuring the quality of the data recorded by general practice. FirstHealth collects data from all practices. A Clinical Policy Committee determines the data to be collected. The data are collected automatically using Structured Query Language (SQL) 'queries'. We were supplied with data from fourteen practices (representing 44 GPs) in the PrimeHealth group of practices, in the Western Bay of Plenty. All practices used computerised clinical

records, twelve using 'MedTech' and two using 'GPDat'. The data collected are shown in Table 1.

### Methods

Each practice dataset was examined for completeness. In the case of demographic data, it was expected that age, gender, ethnicity and smoking status data would be recorded for every patient. To assess the completeness of diagnosis codes, it was necessary to develop a method of estimating a rate of known diagnoses for each practice, and comparing recorded rates with these estimates.

Data for the same practices were downloaded from Health Benefits Limited (HBL) for all laboratory tests and prescriptions for which claims were submitted to HBL for the year April 1997 to March 1998. These data were merged on practice codes to create a set of tables that could be consulted to produce monthly totals of tests and prescriptions submitted for claims, by individual test or prescription item. Each diagnosis code in the practice dataset was considered to see if a lower limit on the number of patients with that diagnosis could be derived from the laboratory or prescribing data available. For example, to determine a minimum number of diagnoses for osteoarthritis a practice should have recorded would require finding a pharmaceutical used exclusively for osteoarthritis, and calculating the average number of prescriptions per month issued by a practice. No such pharmaceutical exists, as the commonest medications for osteoarthritis, the non-steroidal anti-inflammatories, are used in many other conditions. However, for many conditions there is a very tight association between diagnosis and prescription; for instance, insulin is only prescribed for diabetes, and lithium is only prescribed for mania.

The accuracy of estimates for the number of patients with a given diagnosis relies upon the frequency with which a prescription is given for a given condition, and the number of possible agents that may be prescribed. For example, non-insulin dependent diabetes (NIDDM) may be managed with dietary modification only. Cases managed in this way will generate no prescriptions, and estimates of cases based on prescribing analysis will be low.

**Table 1. Description of collected data.**

Data items collected (numbers)	Diagnoses / Treatments requiring blood tests
Total list size Ages (in bands) Weight/Height/BMI recorded Ethnicity (Maori/Other/Absent) Smoking status (Present/Absent) in age bands Patients >65 with flu shot Patients >65 with diagnosis "flu" (H27) Asthmatics with Peak Flow recorded BP recorded in last 5 years	Group 1 – specific Read code: Warfarin (INR), Hypothyroidism (T4), Epilepsy (anti-convulsant), Polymyalgia Rheumatica (ESR), Lithium Therapy (Li) Diabetes (HbA1c), Hyperlipidemia, Blood disorder, Gout Group 2 – diagnosis + blood test recorded as necessary: Hypertension, Chronic Renal Failure, Chronic Hepatitis
<b>Diagnoses searched for by Read code (numbers)</b> Hypertension, Asthma, NIDDM, IDDM, Heart Failure, CORD, Hypothyroidism, Hepatitis, Depression (reactive, endogenous, with psychosis), schizophrenia, HIV, Chronic Renal Failure, Leukaemia, Ca colon, Ca lung, Ca breast, Ca cervix, Ca stomach, Ca prostate, Ca bladder, Ca brain, melanoma, BCC, SCC, Epilepsy, Parkinson's, Alzheimer's, Multiple Sclerosis, Motor Neurone Disease, Anxiety states, eating disorder, acute lumbar strain, RSI, methadone treatment, B12 deficiency, Gonorrhoea, Gastroenteritis, Strep pharyngitis, Chlamydia, Cataract, Glaucoma, Osteoarthritis, Rheumatoid arthritis, Meningitis (meningococcal, haemophilus), Measles, Rubella, Influenza	

All data elements were tabulated by gender.

The estimate of the number of cases is further complicated by multiple agents. Some NIDDMs are managed with sulphonylureas, some with metformin (the only biguanide available in New Zealand), and some with insulin. Because of the possibility of being prescribed two agents, however, an estimate of the number of cases must use the most frequently prescribed agent or the sum of mutually exclusive agents – no one is prescribed two sulphonylureas. The estimate must then be interpreted as being a minimum, bound on the number of cases that are receiving prescriptions.

Similar analyses were applied to each of the conditions in the data downloaded from the practices. Estimates were constructed to be as valid as possible, and were therefore usually very conservative. In the best possible case, the estimates would logically significantly underestimate the actual numbers of cases of a given condition. The estimated rates of recorded diagnoses were then compared with the actual recorded numbers to see if these estimates could be used as useful measures of data quality at this stage in the development of diagnosis recording in general practice.

## Results

After examining possible methods of data accuracy determination for each of the recorded data elements, we constructed the following set of data quality indicators. The indicators fell into three groups: measures of demographic data completeness (including smoking status recording), measures of diagnosis coding adequacy, and a gender by diagnosis composite index. The demographic data quality indicators are described in the top section of Table 2, and measure the completeness of gender, date of birth, ethnicity and smoking status recording. From the analysis of diagnoses, we selected a set of diagnosis data quality indicators. They have been chosen using two criteria. The first is that they are valid, that is, their construction leaves little doubt that they are measuring data quality. Typically, they do not rely upon any unreasonable assumptions and involve tight binding between diagnoses and pharmaceuticals or laboratory tests. The second is that they are sensitive. There is little point using an indicator that every practice passes already, as there is no further information to be gained in subsequent data collection. Neither is there any benefit in including measures based on diagnoses with low prevalence (for example, glaucoma, as evidenced by low prescribing rates) since the scoring of the indicator is problematic when there are no cases. However, indicators that no practice presently passes may be useful if we are certain the indicator is valid.

The set of indicators has been constructed with a view to including measures of the accuracy of coding of the most prevalent chronic conditions when possible. Fortunately, reasonably strong indicators are available for diabetes and ischaemic heart disease (IHD).

**Table 2. Data Quality Indicators.**

Name of data quality indicator	Description
<b>Demographic data indicator</b>	
Gender	% records with gender entered
DOB (date of birth)	% records with date of birth entered
Ethnicity	% records with ethnicity entered
Smoking	% records (aged 16 or over) with smoking status entered
<b>Diagnosis type indicators</b>	
Asthma	<b>Criterion for 'pass' score</b> exceed maximum monthly prescriptions for greater of (average number of bronchodilator scripts per month) and (average number of inhaled steroid scripts per month)
NIDDM	exceed (average number oral hypoglycemic scripts per month)
IDDM	exceed (average number insulin scripts per month)
IHD	exceed (average number nitrate scripts per month)
Hypothyroidism	exceed (average number thyroxine scripts per month)
Bipolar	exceed (average number lithium scripts per month)
Parkinsons	exceed (average number levodopa scripts per month)
Warfarin	exceed (average number of INR tests per month) / 8
Digoxin	exceed (annual number of digoxin levels) / 2
<b>Gender coding indicator</b>	
Sexdiag	No gender errors for ca cervix, ca ovary or ca prostate.

Because of the weak linkages between the three datasets (practice data, laboratory test claims data and prescription claims), some of these indicators are only useful as measures of relatively serious under-recording of diagnoses. We have had to construct indicators that use conservative criteria to ensure high validity. It will be possible to significantly improve estimates of diagnosis rates if and when script/patient or laboratory test/patient linking becomes available. The proposed set is shown in the middle section of Table 2. The last entry in Table 2 describes a composite 'gender by diagnosis' measure. All practices have passed this index in our analysis, however, it has been included because it is a

different type of indicator to the previous two. The indicator is passed if there are no cases of male gender recorded for diagnosis of cancer of the cervix or cancer of the ovary and no cases of female gender for cases of cancer of the prostate. Breast cancer is not included because of the possibility of male gender (1% of cases of breast cancer).

To simplify reporting of results, we have chosen to use a pass/fail scoring system for tracking the quality of both demographic and diagnosis data over time. This requires the setting of thresholds for the demographic data items. We have chosen 100% as the threshold in the first instance, but this might be relaxed for ethnicity coding (to say 95%).

A practices data quality score is then simply the sum of their passes, to give a score out of 14. This is scaled to 100 for reporting purposes. The score for a network of practices is then the average value of the practices' scores, weighted by practice size.

Table 3 describes the performance of each practice on the 14 indicators, and gives a percentage score for each practice, ranging from 3/14 to 9/14.

**Table 3. Data quality summary table.**

Practice	Gender	DOB	Ethnicity	Smoking	Asthma	NIDDM	IDDM	IHD	Hypothyroidism	Bipolar	Parkinson's disease	Warfarin	Digoxin	Sexdiag	Total %
1	Y	Y	N	N	Y	N	N	Y	Y	Y	Y	N	Y	Y	64%
2	Y	Y	N	N	Y	N	Y	Y	N	Y	N	N	Y	Y	57%
3	Y	Y	N	N	Y	N	N	Y	N	Y	Y	Y	N	Y	57%
4	Y	Y	N	N	N	N	N	N	Y	N	N	N	N	Y	28%
5	Y	Y	N	N	Y	N	Y	Y	Y	N	Y	N	Y	Y	64%
6	Y	Y	N	N	Y	N	N	Y	N	Y	N	N	Y	Y	50%
7	Y	Y	N	N	Y	N	N	Y	N	N	Y	Y	N	Y	50%
8	Y	Y	N	N	Y	N	N	Y	N	Y	Y	Y	N	Y	57%
9	Y	Y	N	N	N	N	N	N	N	N	N	N	Y	Y	28%
10	Y	Y	N	N	Y	N	N	N	N	Y	Y	N	N	Y	42%
11	Y	Y	N	N	Y	N	N	Y	N	N	Y	Y	Y	Y	57%
12	Y	Y	N	N	N	N	N	N	N	N	N	N	N	Y	21%
13	Y	Y	N	N	Y	N	N	Y	Y	Y	Y	Y	N	Y	64%
14	Y	Y	N	N	N	N	N	N	N	N	N	N	N	Y	21%

Y = yes; N = no.

## Discussion

Although the estimates of numbers of diagnoses were very conservatively constructed, it was interesting to see how many practices did not record the expected number of diagnoses. This suggests that there is significant room for improvement in diagnosis recording in these practices, which is not at all surprising given the relative short time that diagnosis coding has been available. More importantly, the low scores obtained by most practices indicates that the above method of measuring data quality has some practical use in providing practices with feedback on their levels of diagnosis recording.

One possible method for determining data completeness would have been by a survey of a random selection of each doctor's notes. However, this would have been time consuming, very expensive, and not useful as a practical tool for ongoing monitoring of data quality. By using claims data, coupled with automatic downloads from practice computers, data quality feedback can be given with no requirement for any extra work by the practice team, other than running a programme.

We conclude that non-invasive data quality measures may be useful in providing feedback to GPs as part of a data quality improvement cycle. The sensitivity of this method will decline as data quality improves. However, the potential for constructing more sensitive measures of data quality will improve substantially when laboratory testing and prescribing can be allocated to individual patients.

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**Correspondence.** Barry Gribben, Director RNZCGP Research Unit, Department of General Practice and Primary Health Care, University of Auckland, PO Box 92019, Auckland. Fax: (09) 834 2970; Email: b.gribben@auckland.ac.nz

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Almost a decade after it was found that folic acid could prevent the development of neural tube defects such as spina bifida, three researchers have received the Kennedy Foundation international award for scientific achievement for the discovery.

The award was made to Professor Nicholas Wald of Barts Hospital, Professor Richard Smithells, emeritus professor of paediatrics at Leeds University, and Dr Andrew Czeizel of the Budapest National Institute of Hygiene for key studies that led to the eventual identification of the beneficial effects of folic acid.

The award came four years after the United States acted on the research and began to fortify flour with folic acid. The UK Department of Health last month launched a three month consultation before deciding whether to require manufacturers to add folic acid to flour in the same way.

For Professor Wald, however, the evidence for fortification has been overwhelming for some time. "There is now conclusive evidence that if women consume more folic acid there is a substantial reduction in the changes of having a baby with spina bifida," he said. "Women need to take it before they become pregnant, so putting it in flour is the most effective way of preventing this disorder in the population, and the Americans have been doing it since 1997."

Roger Dobson, *BMJ* 2000; 321: 400.

"Basic research" said Werner von Braun "is what I'm doing when I don't know what I'm doing." Clearly this was an alarming statement, coming as it did from someone whose main research interest was lighting matches under huge quantities of explosive fuel. I suppose you could tell he was good at it, because he was still around to propose the next development, and the next... But, perhaps his remark had an effect. Certainly, 50 years or so later, a paraphrase would read rather differently – perhaps something along the lines of "Basic research is something that I can't get funding for unless I already know the answer and have already done half the experiments".

John A Lee, *The Lancet Oncology* May 2000; 24.



# Delays in the investigation of allegations of child sexual abuse in the Wellington city district 1995-1996: a retrospective study

Sarah Halsted, *Medical Student*; Dawn Elder, *Senior Lecturer in Paediatrics, Department of Paediatrics, Wellington School of Medicine, Otago University, Wellington.*

## Abstract

**Aims.** To determine the duration of the statutory investigation process after referral of alleged child sexual abuse and to assess which components of this process are most prone to delay.

**Methods.** Retrospective review of police, Child Youth and Family (CYF) and medical records for 123 young persons <17 years old for whom a referral regarding alleged sexual abuse was made to the Wellington Serious Abuse Team from January 1995 to December 1996.

**Results.** There were 82 (66.7%) females and 41 (33.3%) males referred. Maori and Pacific Island children were over-represented in the sample. The median time from

referral to evidential interview or diagnostic interview was 47 days. This period was longer for children <5 years of age (66 days) compared with children ≥5 years of age (45.5 days), although this difference was not statistically significant. Although 53.3% of children alleged genital contact, only 26% were referred for a medical assessment. The time from initiation of investigation to completion was a median of 141 days. Reasons for delay were difficult to delineate but appeared to relate to inadequate staffing.

**Conclusions.** There is an unreasonable delay in the investigation of alleged child sexual abuse. This is particularly concerning in younger children.

NZ Med J 2001; 114: 33-5

Child sexual abuse is a serious and significant problem. At least 10% of New Zealand children and young persons are exposed to inappropriate and unwanted sexual experiences before the age of sixteen years.<sup>1</sup> Although many cases of alleged child sexual abuse are referred for investigation each year in New Zealand, the number of substantiated complaints is unknown. Also, as sexual abuse cases have not been differentiated from other forms of child abuse in statutory agency statistics, the number of cases presenting for investigation is not accurately known, making it difficult to appropriately plan multidisciplinary investigative services.

Poorly co-ordinated and repeated investigations can have deleterious effects on the child.<sup>2</sup> In New Zealand, Serious Abuse Teams (SATs) have been established to investigate allegations of child abuse, including child sexual abuse. These teams are made up of Criminal Investigation Branch (CIB) Police and Child, Youth and Family (CYF) social workers who may be assisted by paediatricians and other allied health professionals in the investigation of these complaints.

Although the development of the multidisciplinary approach to the investigation of allegations of child sexual abuse has greatly improved the assessment process, significant concerns remain about delays. Allegations should be investigated expeditiously for the sake of both alleged victim and alleged perpetrator. Since the allegations are often difficult to prove, it is important that children's evidence is as accurate as possible, as in many cases the child's disclosure may be the only evidence available on which a decision regarding prosecution may be based. If medical assessment is required, children should be seen as soon as possible after the alleged event.

There has been a considerable body of research on the prevention of, counselling for and physical signs of child sexual abuse, but fewer studies have looked at how long it takes multi-disciplinary teams to investigate complaints of sexual abuse. In practice, it is apparent that there are significant delays in this process in New Zealand but no formal review has been undertaken. The aim of the present study was to examine retrospectively, the length of time taken by a central city SAT to investigate complaints of child sexual abuse, and to see if reasons for delay could be determined.

## Methods

Data from 123 sexual abuse complainants were obtained from the records of the police, CYF and medical files. All subjects were under seventeen years of age and had been referred to the Wellington City region SAT between 1 January 1995 and 31 December 1996. Neither the complainant nor their parents were re-contacted.

Child sexual abuse was defined as the involvement of dependent, developmentally immature children and adolescents in sexual activities that they do not fully comprehend, are unable to give informed consent to, and that violate the social taboos of family roles.<sup>3</sup> The sexual activities were defined as contact abuse, including genital penetration and genital touching, or non-contact abuse including the viewing of masturbation and pornography. Acts of voyeurism and exposure were not included in the study as they were not referred for investigation to the specialist child SAT. Ethical approval was obtained from the Wellington Area Ethics Committee. Approval for the study was also obtained from the New Zealand Police, and CYF (previously the New Zealand Children and Young Persons and their Families Agency).

Details extracted included demographic data (age, sex, race), the nature of the allegations and details of the timing of each stage of the investigation process. The latter included the dates of initial referral, SAT intake, initial interview or meeting with the complainant and his/her caregivers, evidential interview or diagnostic assessment, medical assessment and the starting date of any court proceedings. Reasons for the delay were documented where possible. The endpoint of the investigation was taken as either the completion of the court process or a decision to end the investigation because of insufficient evidence. Data about the alleged perpetrator were limited (by the ethics committee) to their age and whether he/she was known to the child.

All information collected was transferred to the computer data management programme Epi-Info. Time (in days) was calculated for most major time points in the investigation procedure. Medians were calculated for each of these time points. ANOVA was used to compare differences in the time taken to investigate children under five years old, compared with the total cohort.

## Results

123 cases of alleged child sexual abuse were available for review over the time period. A further unspecified number of cases could not be assessed because files were missing or deemed too confidential. There was no database in place that would allow us to accurately determine how many cases were missing. The cases assessed therefore represent the majority but not all cases referred to the SAT team over the two-year period. Some data from the reviewed 123 cases were missing due to incomplete documentation.

There were 82 female complainants (66.7%) and 41 males (33.3%). All age ranges from one year on were represented, with the peak being at three to six years. Maori and Pacific

Island children were over-represented in the cohort, compared with the normal Wellington population racial distribution (Figure 1). Caucasian children made up 67.1% of the cohort, Maori children 25.6%, Pacific Island children 6.1% and other racial groups (mostly Asian) 1.2%. Information on race was unavailable for 41 children.

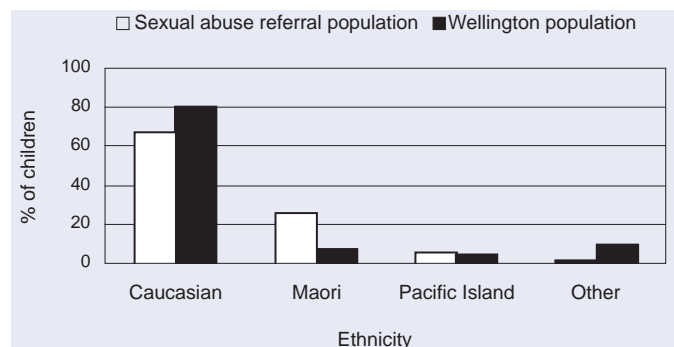


Figure 1. Ethnicity of sexual abuse referral population compared with the ethnicity of the Wellington City population.

The majority (53.3%) of allegations involved genital contact. Non-genital contact allegations were made in 28.3% of cases and 9.2% concerned non-contact offences. In a further 9.2% cases, the type of contact could not be determined, usually because of limited disclosure. Despite 53.3% of the children alleging genital contact, only 26% were referred for a medical assessment.

Most children (95.9%) knew the alleged perpetrator. This information was, however, only available for 74 (60%) of the cases. Figure 2 shows the age of the alleged perpetrator. This information was only available for 51 (41%) cases. There were two age peaks, one in the adolescent age group (10-19 years) and one in the 30-49 age group. The latter group most likely represents parents, defacto parents or other primary caregivers.

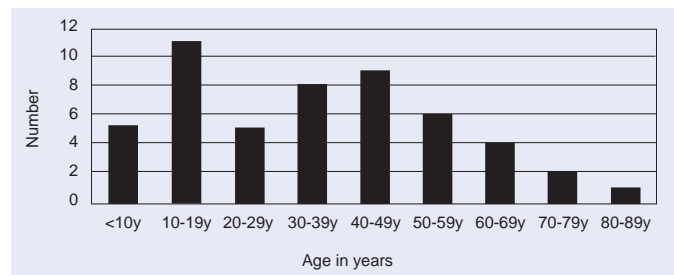


Figure 2. Age of the alleged perpetrator.

Table 1 shows the time from initial referral of sexual abuse to, respectively, the initial SAT intake, the first family interview, the first evidential or diagnostic interview, the first medical interview, and to either the completion of the investigation process or the court process. The median time from initial referral to the initial SAT intake was six days, to the first family interview 20 days, to the first evidential or diagnostic interview 47 days, and to the first medical interview 29 days. The median time for initial referral to when either the investigation or court process was complete was 141 days. Delays were not necessarily related to a need for a preliminary investigation before initiating family contact, as this was required in only 30.9% of the 58 cases for which this information was available.

Figure 3 shows a box and whisker plot for the amount of time taken to investigate allegations in children under five, compared to those five years and older, from first referral to the first evidential or diagnostic interview. The time taken to

investigate children under five (median 66 days) was longer than to investigate complaints regarding children five years and older (median 45.5 days), although this difference was not statistically significant. There was insufficient information to determine the cause for the delays.

Table 1. Time from initial referral.

Investigation	Median (25th, 75th Centile) n=days	Maximum recorded n=days	Number for whom data available
Referral to SAT	6 (2,14)	221	107
Family Interview	20 (7,48)	197	107
Evidential Interview	47 (17,84)	266	72
Medical Examination	29 (1,92)	392	32
Court/NFSA*	141 (97,228)	708	100

\*NFSA - No further SAT action.

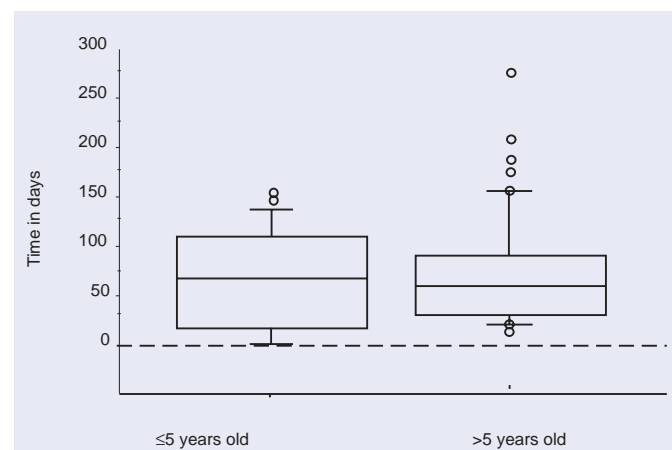


Figure 3. Days from referral to evidential interview for children five years and under compared with over five years. Each plot represents the median days, 25th and 75th percentiles, and outliers.

## Discussion

This study has shown considerable delays in the investigation of complaints of child sexual abuse in the Wellington City area. This delay was longer for children under five than older children. A median of 47 days (almost 7 weeks) was taken from the initial complaint of child sexual abuse to the first diagnostic or evidential interview, compared with the recommended time period of 72 hours (3 days).<sup>4</sup> After a period of seven weeks, a clear disclosure from a younger child at evidential interview is much less likely.

A major concern was the amount of missing data. There were significant variations between individual workers from both disciplines in the quality of record documentation. We were also unable to easily source a complete database of children referred for investigation by the SAT. This has made interpretation of our results difficult and means it is not easy to define the workload of the police and CYF workers in the SAT.

Females were more likely to be referred regarding allegations of sexual abuse than males, and Maori children were over-represented. It is not clear if this represents a higher incidence of sexual abuse in Maori or an increased rate of reporting and referral for investigation.

The limited available profile of the alleged perpetrators is comparable to other studies, although most reports document the offender's relationship to the child rather than their age, as the latter is not always known accurately.<sup>5,6</sup> As most complainants knew the alleged offender, continued contact can pose a risk for the child, confirming the importance of fast-tracking the investigation. The number of allegations involving

adolescent offenders is concerning as these young people may go on to further violent offending, and are likely themselves to have a past history of victimisation, including physical and sexual abuse and neglect.<sup>7</sup>

The low rate of referral for a medical assessment is concerning. All children and young persons, for whom significant abuse is alleged to have occurred, should have a medical assessment by an appropriately trained doctor to screen for other forms of abuse, untreated medical problems and psychological and developmental sequelae, as well as physical signs that may be a result of the alleged assault. The examining doctor should determine whether or not a full genital examination is required and have the opportunity to discuss this with the complainant and caregivers. Other medical conditions that can mimic sexual abuse should be excluded.<sup>8</sup> Children appear to disclose their abuse on a continuum so a decision about whether or not a medical assessment is required based on the initial disclosure alone may be misleading.<sup>9</sup>

San Lazaro et al in the UK documented a range of 14 to 552 days to completion of the investigation.<sup>10</sup> Such delay may mean insufficient evidence is gathered to support a charge being laid. Also, the alleged perpetrator, if innocent, is never completely exonerated. As well as delays in investigation, further delays occur before the case is heard in court. Martone et al reported an average delay in sexual abuse cases being resolved by trial in the USA of twelve to sixteen months,<sup>11</sup> while San Lazaro et al reported a median time of 260 days (range 14-552) from the start of the investigation to trial.<sup>10</sup> Many American states now have laws allowing for a faster resolution of criminal cases involving victims or witnesses who are children.<sup>11</sup> Despite the availability of videotaped evidence in New Zealand, children may still be expected to appear in court to give verbal evidence and to be further questioned and cross-examined on events that happened months previously.

Few reasons for delay have been documented, but anecdotal evidence suggests staffing and resourcing issues are important. The police team at the time of the study was often diverted to other CIB investigations. Delays also occurred when staff were on sick leave or training courses, as there were insufficient trained personnel to cover leave. Although resourcing has improved in the last year, delays still occur with all aspects of the investigation, including the availability of an appropriately trained doctor to perform a medical assessment. Investigation should always be by personnel with specialist training. Child sexual abuse

investigations undertaken by specialist police child sexual abuse units are more likely to result in the offender being interviewed and charged.<sup>12</sup> Investigation by a multidisciplinary team including police, social workers, paediatricians and assistant state attorneys has been shown in the USA to decrease the number of victim interviews required and increase the likelihood of the perpetrator being identified and charges being pressed.<sup>2</sup>

Sexual abuse appears to be experienced by at least 10% of our New Zealand population of children and young people.<sup>1</sup> There is good evidence now that for many of those affected there are significant mental and physical health sequelae.<sup>13-15</sup> It is time that resources for the services charged with investigating and managing child sexual abuse became appropriate to the extent and seriousness of the problem.

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**Correspondence.** Dr Dawn Elder, Wellington School of Medicine, PO Box 7343, Wellington South. Fax: (04) 385 5898; Email: delder@wnmeds.ac.nz

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Publication of clinical research has resulted in legal action being initiated in Giessen, Germany. A team of paediatric intensive-care specialists reported an outbreak of sepsis from contaminated disinfectant leading to the death of two children and to severe disability in one child between October 1996, and March 1999. This report was widely covered by the German mass media and came to the attention of prosecution authorities in Giessen. State attorney Michael Wenzel told *The Lancet* that investigations had been started as a routine measure. No expert opinion has been given.

There have been many stories in the media, alleging that hygiene standards in Germany are lower than those in comparable countries. Jürgen Hessemann, head of the Max von Pattenkover Hygiene Institute of Munich University stated there was no reason to believe that hygiene standards in German hospitals are lower than those in other western countries. But Henning Rüden of the national reference centre for hospital hygiene in Berlin stated that Germany's hygiene science lags behind that of neighbouring countries.

Georg Röggl. *Lancet* 2000; 356: 574.

Clinical trials are intrinsically no more threatening than any other form of treatment. In some ways, they are better. Standards of care and consent are often superior. What most people worry about is uncertainty being discussed out loud. Yet medical science and practice never was built on certainty. We have better understanding of uncertainty than ever before, and better methods for grappling with it. The demystification of the doctor, which is supposedly the risk which attaches to admitting uncertainty, has already happened.

Richard Ashcroft. *BMJ* 2000; 320: 1686.



## Clinical use of beta-blocker therapy in patients with heart failure: a practical guide

Robert N Doughty, *National Heart Foundation BNZ Senior Fellow, Department of Medicine, School of Medicine, The University of Auckland, Auckland*; A Mark Richards, *National Heart Foundation Professor of Cardiovascular Studies, Department of Medicine, Christchurch School of Medicine, Christchurch*.

NZ Med J 2001; 114: 36-8

Over 14 000 patients have been involved in 28 randomised, controlled clinical trials of the effects of beta-blockers in patients with heart failure (see accompanying editorial). These trials have provided clear evidence of the clinical benefits of beta-blockers in such patients. The data are at least as robust as the evidence guiding the use of ACE inhibitors in patients with heart failure.<sup>1</sup> Consequently, beta-blockers have the potential to have a major impact in the management of chronic heart failure. Local New Zealand guidelines for beta-blocker use have yet to be introduced, although the National Heart Foundation Heart Failure Guidelines are currently being revised to incorporate their use. Beta-blockers do have the potential for adverse effects and their safe use relies on careful patient selection, appropriate initiation and titration and clinical monitoring. This article provides practical points to consider when translating the trial data into clinical practice in New Zealand.

### Patient Selection

Selection of patients with heart failure for beta-blocker use is key to their safe use. Patients should be similar to those enrolled in the clinical trials from which the efficacy and safety data are derived. Patients should:

- have chronic stable heart failure with left ventricular (LV) systolic impairment
- have mild-moderate symptoms (NYHA functional class II-III)
- be clinically stable on adequate doses of ACE inhibitor and diuretic (eg enalapril 10 mg bid, or equivalent, and the minimum dose of loop diuretic necessary to eliminate signs of volume expansion). In practice, clinical stability will usually mean that patients will have had no change in their symptoms and have not required major changes in treatment, particularly diuretic regimes, for one month.
- have no other specific contraindications to beta-blockers, such as reversible airways disease or second/third degree heart block or sick sinus syndrome (in the absence of a permanent pacemaker).

### Specific Clinical Points

**NYHA functional class.** Currently, the clinical trial evidence does not support the administration of beta-blockers to patients with NYHA class IV symptoms or those who are clinically unstable. Often such patients are hospitalised and thus initiation of beta-blockers is not generally appropriate during hospitalisation for an exacerbation of heart failure. However, many such patients improve with treatment and thus should subsequently be reassessed for suitability for a beta-blocker. Usually this means review in an out-patient setting some weeks after hospital discharge.

A recent open, non-randomised study reported the tolerability of carvedilol in patients with heart failure from a

tertiary referral centre in Sydney.<sup>2</sup> The clinical experience from this study suggested that those patients with NYHA class IV symptoms are more likely to develop adverse events during initiation of carvedilol than those with milder symptoms. Relatively few patients with NYHA class IV symptoms have been enrolled in the randomised controlled trials completed and reported to date. However, the recently completed COPERNICUS Trial,<sup>3</sup> involving patients with severe heart failure, has shown a significant survival benefit with carvedilol (see below).

**Concomitant treatment.** As mentioned, patients should be receiving an ACE inhibitor (or perhaps angiotensin II antagonist if intolerant of an ACE inhibitor) and diuretic. Dosages of the ACE inhibitor should be optimised according to current clinical practice guidelines prior to initiating the beta-blocker (eg enalapril 10 mg bid, captopril 25-50 mg tid, cilazapril 5 mg daily, quinapril 10 mg bid, lisinopril 20 mg daily).<sup>4</sup> Thus, it is not recommended to start a beta-blocker at the expense of maintaining adequate ACE inhibitor dosages.

Some patients may be intolerant of both ACE inhibitors and angiotensin II antagonists and, while such patients have not been the subject of specific randomised trials, it would appear prudent to offer these patients beta-blocker therapy. Similar selection should be used, with the patient's symptoms and signs of congestion controlled with a loop diuretic prior to initiation of the beta-blocker.

The RALES Trial<sup>5</sup> showed that spironolactone, used in addition to ACE inhibitor and diuretic, improved survival in patients with moderate to severe heart failure. The patients in this study had severe heart failure: they were required to have NYHA class III or IV symptoms at the time of entry into the trial and must have been in class IV within the previous six months. Only 10% of the patients in this trial were receiving beta-blocker therapy, thus the effects of the combination of beta-blockers and spironolactone are unclear. The NHF Heart Failure guidelines are being updated to include the use of spironolactone.

**Blood pressure.** In general, there is little clinical experience with beta-blocker therapy in patients with low blood pressure. Both CIBIS II<sup>6</sup> and MERIT-HF<sup>7</sup> excluded patients with a systolic blood pressure less than 100 mmHg. Mean systolic blood pressure at entry to these two trials was approximately 130 mmHg. The US Carvedilol Trials<sup>8</sup> allowed entry of patients with systolic blood pressure as low as 85 mmHg. While mean systolic blood pressure at randomisation was lower (115 mmHg) than in CIBIS II<sup>6</sup> or MERIT-HF,<sup>7</sup> it is uncertain how many patients had blood pressure at the lower end of the entry criteria. Thus, most clinical trial experience, at present, is for patients without low blood pressure.

**Left ventricular ejection fraction.** The beta-blocker trials to date have only included patients with left ventricular systolic impairment. Beta-blocker therapy may be of value for those patients who have heart failure with preserved systolic function (so called 'diastolic dysfunction') via such



mechanisms as prolongation of diastolic filling, although definitive clinical trials have yet to be carried out in this patient subgroup. Imaging of the heart is thus recommended to confirm LV systolic impairment, although accurate quantification of the LV ejection fraction is not essential and will depend on local practice patterns.

Patients with a very low left ventricular ejection fraction should not be excluded from consideration of beta-blocker therapy, as they also have the potential to gain from such treatment. Monitoring of the response in LV ejection fraction to beta-blocker therapy is not required, since lack of improvement in LV ejection fraction does not imply lack of potential long-term clinical benefit. Thus, routine repeat assessment of LV size and function, for example with serial echocardiography, is not recommended.

## COPERNICUS Trial

This trial is the first randomised, placebo controlled trial of the effects of beta-blockers in patients with severe heart failure. The trial included patients with an LV ejection fraction <25% who were receiving ACE inhibitor (or angiotensin II antagonist) and diuretic. Although patients could have symptoms of dyspnoea at rest or with minimal exertion, certain stability criteria had to be fulfilled at entry into the study, including systolic blood pressure > 85 mmHg (seated), no pulmonary rales or peripheral oedema and weight change of <1.5kg within three days of starting the study drug. This trial thus includes a sicker group of patients with more severe symptoms than those previously enrolled in the trials. The trial was stopped early due to a significant survival benefit with carvedilol in March 2000 and the results were presented at the European Society of Cardiology Meeting in August 2000.<sup>3</sup> Full publication of the results will allow clearer recommendations regarding the initiation of carvedilol in sicker patients. Although these recommendations will include early initiation of beta-blockade in patients with more severe symptoms, it is important to carefully assess each patient for signs of clinical stability (as used in this trial) before the beta-blocker is started.

## Initiation and Titration of Beta-blocker Therapy

Once the patient has been selected for a beta-blocker, a clear explanation of the planned treatment should be given to the patient. This is important, as there is the potential for patients to feel slightly worse early during treatment. Patients should not expect rapid, short-term symptomatic improvement, but should be aware that such improvement may come in the intermediate or longer term and that beta-blocker therapy carries survival benefit.

In the MERIT-HF Study,<sup>7</sup> 196 of the 1990 (9.9%) patients randomised to receive metoprolol had their study drug withdrawn due to an adverse event (including patient decision). However, in only 64 patients (3.2%) was the reason for withdrawal worsening heart failure, suggesting excellent tolerability of beta-blockade.

## Type of Beta-blocker

Survival benefit with beta-blockers has been demonstrated with bisoprolol,<sup>6</sup> metoprolol<sup>7</sup> and carvedilol.<sup>3,8</sup> The relative reduction in mortality observed in the US Carvedilol Trials appeared greater than with bisoprolol<sup>6</sup> or metoprolol<sup>7</sup> (65% vs 34% respectively). Although these agents have different properties, the overall relative risk reduction in the COPERNICUS Trial<sup>3</sup> (35%) was similar to that in CIBIS II<sup>6</sup> and MERIT-HF.<sup>7</sup> Carvedilol and metoprolol are being directly compared in the ongoing 'Carvedilol Or Metoprolol European Trial' (COMET).

These three agents have different pharmacological properties and beta selectivity (Table 1). The metoprolol preparation used in the MERIT-HF study,<sup>7</sup> metoprolol CR/XL, produces a relatively constant blood level for 24 hours, compared with the conventional formulation of metoprolol.<sup>9</sup> Currently, only carvedilol is registered for use in heart failure in New Zealand. Metoprolol CR tablets are available but the drug is not specifically registered for use in heart failure, although applications are underway. Carvedilol became commercially available in New Zealand from 1st July 2000, although it is not currently subsidised (personal communication, Roche pharmaceuticals).

**Table 1. Initiation and titration regimes used in the clinical trials.**

Trial	ANZ Carvedilol <sup>10</sup>	CIBIS II <sup>6</sup>	MERIT-HF <sup>7</sup>
Study drug	Carvedilol (non-selective, vasodilating)	Bisoprolol (beta <sub>1</sub> -selective)	Metoprolol CR/XL (beta <sub>1</sub> -selective)
Open run-in phase	Yes	No	No
Initial test dose	3.125 mg	1.25 mg	12.5-25 mg
Titration period	6 weeks	11 weeks	6 weeks
Maximum dose	25 mg bid	10 mg daily	200 mg daily
Mean dose of beta-blocker at end of follow-up*	20.5 mg bid	8.6 mg	159 mg
% receiving maximum dose of beta-blocker*	48%	43%	64%

\*dosages refer to those in the active treatment arms of these studies; ANZ=Australia-New Zealand; CIBIS=Cardiac Insufficiency Bisoprolol Study; MERIT-HF=Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure; bid=twice daily.

## Initiation of Beta-blocker Therapy

Once patients have been selected for beta-blocker therapy according to the above criteria, beta-blockers can usually be initiated in an out-patient setting. In general, an experienced physician should supervise the patient. The beta-blocker should be started at low dose, for example metoprolol 5-10 mg, or carvedilol 3.125 mg or 6.25 mg. In practice at present in New Zealand, funding issues and availability of low-dosage preparations of beta-blockers particularly hampers this early stage of treatment. The first dose can usually be administered in an outpatient clinic, but the patient should be observed for about two hours, with recording of blood pressure and heart rate. If blood pressure and heart rate are satisfactory then the same dose can be dispensed for the patient to continue. Experienced nurse practitioners may provide an important role in the future for initiation and titration of beta-blocker treatment.

## Subsequent Dose Titration

Following initiation of treatment, further titration can continue, with dose increments at approximately fortnightly intervals, according to tolerability. The titration regimes used in the clinical trials are shown in Table 1. The patient should be clinically assessed before each dose change. Possible adverse effects include: bradycardia, hypotension, worsening heart failure and AV block. Signs of increasing congestion may be controlled with adjustment of diuretic dose and do not necessarily imply long-term intolerance of the drug. The dose of beta-blocker should not be increased further until the symptoms have resolved. However, symptomatic hypotension is more difficult and usually suggests intolerance. Some patients may tolerate lower doses of the beta-blocker with acceptable blood pressure and no symptoms, and may be maintained on these lower doses. With this graduated approach, 70-80% of patients should be

satisfactorily established on maintenance treatment with the dosages employed in the clinical trials (eg carvedilol 25 mg bd, metoprolol equivalent of 200 mg per day).

### How should patients established on beta-blocker therapy be monitored?

Optimal use of beta-blockers in heart failure requires monitoring through regular review, in order to reproduce the safety and tolerability demonstrated in the published trials. Once established on the beta-blocker, review should be continued at three monthly intervals, and if the patient remain stable, follow-up visits may be reduced to six monthly, provided clear instructions regarding warning signs and symptoms of decompensation or side-effects are given. Patients should be encouraged to present early should these problems emerge. If the beta-blocker is interrupted at any stage for more than about two weeks, it is recommended that the agent be recommenced at the low initiating dose and subsequent up-titration phases repeated.

### Management of Patients with Worsening Heart Failure

A patient established on a beta-blocker may deteriorate, for example, with worsening clinical congestion, as can any patient with heart failure. Such exacerbations do not necessarily imply intolerance of the beta-blocker. As in any patient with an exacerbation of heart failure, specific causes or precipitants should be sought, rather than immediate implication of the beta-blocker. The general aim should be to continue the beta-blocker, if possible, and to adjust the other medications, such as diuretics, as required. If intravenous inotropes are required, dobutamine may be less effective due to blockade of the beta-receptor sites. Thus, alternative inotropes, such as milrinone, should be considered. Dose reduction of the beta-blocker may be considered, particularly if relative hypotension is a problem, although consideration should be given to subsequent up-titration once the patient is stable.

### Conclusions

Appropriately prescribed beta-blockers will have a major impact in the management of chronic heart failure. These agents are not necessarily easy to use and care must be taken with patient selection, initiation and subsequent titration of treatment (Table 2). The main message is to start at low dose and increase slowly with regular clinical review, looking for signs of intolerance. Titration may take several weeks or even months. The patient and clinician should be prepared for this slow titration period with frequent clinical monitoring. Education is required to ensure that the patients' expectations of treatment are clear from

the start of treatment. Publications from further clinical trials will help to clarify recommendations for beta-blockers in certain patient groups, such as those with severe symptoms.

**Table 2. Key clinical points for use of beta-blockers in patients with heart failure.**

<b>Patient selection</b>
<ul style="list-style-type: none"><li>• chronic stable heart failure</li><li>• left ventricular systolic impairment (left ventricular ejection fraction <math>\leq 45\%</math>)</li><li>• clinically stable with mild-moderate symptoms (NYHA functional class II-III*)</li><li>• no specific contraindications to beta-blockade (eg asthma, AV block)</li><li>• resting heart rate <math>&gt;50</math> bpm</li></ul>
<b>Initiation</b>
<ul style="list-style-type: none"><li>• start at low dose eg carvedilol 3.125-6.25 mg, metoprolol 5-10 mg</li><li>• administer under supervision as out-patient</li></ul>
<b>Titration</b>
<ul style="list-style-type: none"><li>• clinical review approximately every two weeks and before any dose change</li><li>• increase dose (eg double the dose) if no signs of worsening congestion or hypotension/bradycardia</li><li>• target doses eg carvedilol 25 mg bid, metoprolol 200 mg total daily dose (exact target dose depends on preparation of metoprolol used)</li></ul>
<b>Follow-up</b>
<ul style="list-style-type: none"><li>• once established on beta-blockade, follow-up every 3-6 months (depending on local practice pattern)</li><li>• clear instructions for patient regarding symptoms and signs of worsening congestion/dizziness and need for early presentation of symptoms.</li></ul>

\*Definition of NYHA functional class II = slight limitation of physical activity, comfortable at rest but ordinary physical activity results in fatigue or dyspnoea; NYHA functional class III = marked limitation of physical activity, comfortable at rest but less than ordinary activity causes fatigue or dyspnoea.

**Correspondence.** Dr RN Doughty, Department of Medicine, 4th Floor, Auckland Hospital, Park Road, Auckland. Fax: (09) 302 2101; email: r.doughty@auckland.ac.nz

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## Spontaneous intramural aortic haematoma

**Alan P Whelan, Interventional Fellow; Michael JA Williams, Cardiologist, Dunedin Hospital, Dunedin.**

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Aortic dissection typically originates from a primary intimal tear, with subsequent separation of the aortic wall components and then propagation of blood between these layers. Intramural haemorrhage (IMH) has been increasingly recognised as a specific acute aortic syndrome.<sup>1-3</sup> IMH is thought to arise from spontaneous haemorrhage of the aortic vasa vasorum and is believed to be a possible precursor to overt aortic dissection.<sup>4</sup> We

report a case of spontaneous IMH and review the diagnosis, management and prognosis.

### Case Report

A 74 year old woman presented with sudden onset central chest pain which radiated to the shoulders, arms and epigastrium. She complained of generalised weakness but had no focal neurological deficit. Hypertension had been

noted for some years but no antihypertensive treatment initiated. On admission, the heart rate was 46/min and blood pressure 100/60 mmHg in both arms. The jugular venous pressure was not elevated and auscultation of the heart and chest was unremarkable. Abdominal examination was normal with no epigastric tenderness and no evidence of an abdominal aortic aneurysm. Peripheral pulses were present and equal.

The ECG revealed left ventricular hypertrophy but no acute ischaemic changes. A chest x-ray revealed marked unfolding of the ascending aorta which was unchanged from one taken ten years previously. Cardiac enzyme and troponin-I assays were normal on admission. The clinical diagnosis was acute myocardial ischaemia and the patient was treated with intravenous heparin, glyceryl trinitrate and aspirin. Beta-blockers were withheld in view of the bradycardia. Transthoracic echocardiography revealed left ventricular hypertrophy with normal systolic function and no segmental wall motion abnormality. There was dilatation of the ascending aorta which measured 4.5 cm at the level of the sinotubular junction.

After twelve hours, there had been no ECG changes and troponin-I assays remained normal. The patient had persistent chest pain and subsequently complained of lower back pain. Magnetic resonance (MR) imaging demonstrated aneurysmal dilatation of the ascending aorta and IMH extending from the ascending aorta to the descending thoracic aorta at the level of the diaphragm (Figure 1). A cardiothoracic opinion was sought and medical management advised. Repeat imaging four days later revealed regression of the IMH with increased signal intensity on T1 weighted images suggestive of blood breakdown products (Figure 2). The patient was discharged after ten days, treated with metoprolol CR 190 mg, cilazapril 5 mg/hydrochlorothiazide 12.5 mg, doxazosin 16 mg and felodipine 5 mg daily.

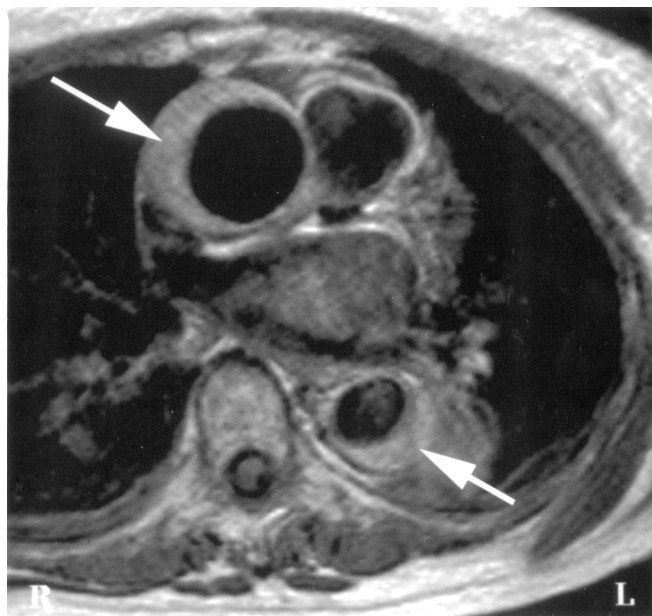


Figure 1. Magnetic Resonance (MR) transaxial T1-weighted image reveals crescentic intramural collections within the ascending and descending aorta (arrows). The signal intensity is similar to that of muscle suggesting acute haemorrhage. The aortic luminal shape is preserved and ECG gated multi-slice/multi-phase MR imaging failed to demonstrate flow within the haematoma.

Two weeks later she re-presented with anterior chest pain of sudden onset. Clinical examination was unchanged and the blood pressure was 94/38 mmHg in both arms. Urgent MR imaging revealed extension of the IMH with luminal

distortion of the ascending aorta (Figure 3). MR pulse sequences suggested flow within the haematoma and the presence of an intimal flap. The findings were consistent with dissection of the ascending thoracic aorta and the patient was referred for surgery. At surgery, there was a 3 cm intimal tear at the sinotubular junction with extensive intramural haemorrhage. The ascending aorta was replaced with a woven Dacron graft without complications. The patient was discharged two weeks following surgery and has remained well.

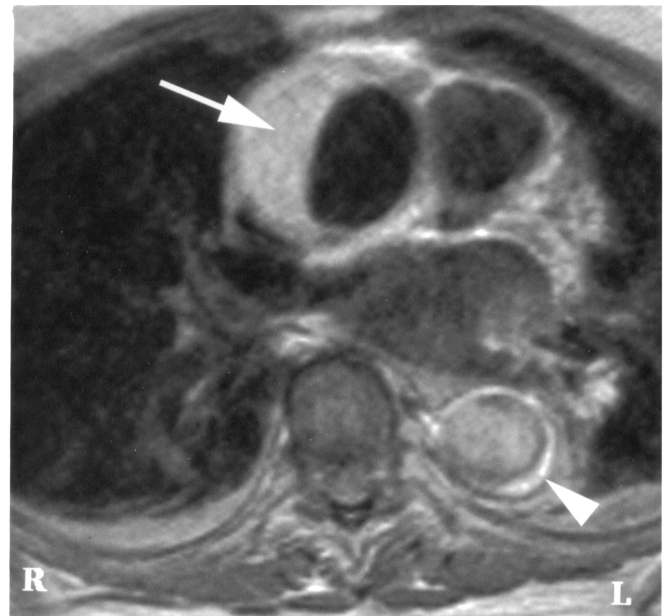


Figure 2. Transaxial T1-weighted scan performed four days later shows partial resolution of the intramural haematoma within both the ascending and descending aorta. Signal intensity within the ascending aorta haematoma has increased due to the accumulation of methaemoglobin as blood products are broken down (arrow). There are moderate bilateral pleural effusions posteriorly.

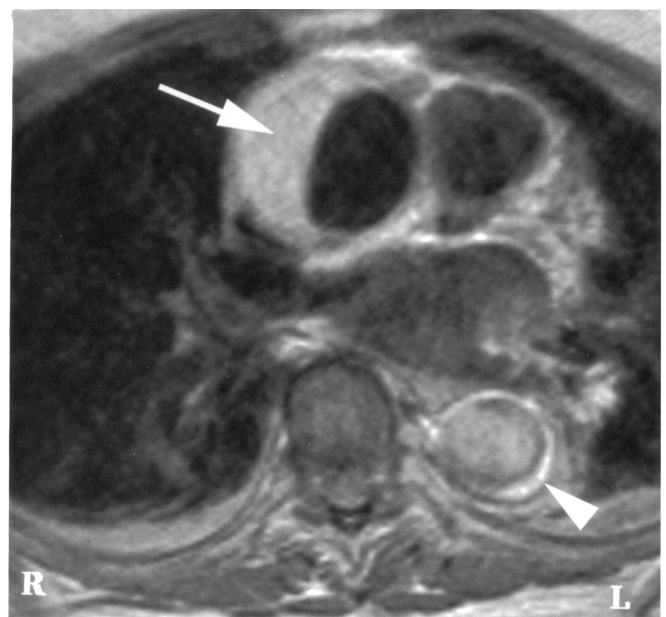


Figure 3. Transaxial T1-weighted scan demonstrates marked aortic wall thickening with luminal distortion (arrow). ECG gated multi-slice/multi-phase MR imaging demonstrated flow within the haematoma. The appearances are consistent with Type A aortic dissection. There has been further resolution of the descending aorta intramural haematoma, which now has the high signal intensity typical of the presence of methaemoglobin (arrowhead).



## Discussion

IMH was first described by Kruckenberg in 1920 as "dissection without an intimal tear",<sup>5</sup> and is thought to be initiated by spontaneous rupture of the aortic vasa vasorum with subsequent propagation of subintimal haemorrhage.<sup>4</sup> Necropsy data from two large series of patients presenting with acute aortic syndromes had identified IMH without an intimal tear in 4-13% of patients.<sup>6,7</sup> As imaging techniques have improved, there has been increased recognition of IMH as a distinct entity in patients presenting with an acute aortic syndrome. Clinical series have identified IMH in 13-27% of patients investigated for an acute aortic syndrome, using contrast enhanced computed tomography (CT) scanning, MR imaging or transoesophageal echocardiography (TOE).<sup>2,3,8,9</sup>

The clinical presentation of IMH is similar to dissection of the thoracic aorta and is also categorised as involving either the ascending aorta (Type A) or being confined to the descending aorta (Type B).<sup>10</sup> Patients presenting with IMH are significantly older than those with aortic dissection<sup>3,8,11</sup> and there is a slight predominance of men.<sup>3,11</sup> A previous history of hypertension is present in 80-100% of patients with IMH.<sup>3,8,12-14</sup> Marfan's Syndrome was present in 10-12% of patients in two reports,<sup>3,14</sup> although was not reported in other series.<sup>8,9,15</sup> Abdominal aortic aneurysm was an associated finding in 12-29% of patients.<sup>11,16</sup> In a review of 209 cases, acute aortic regurgitation occurred in 26%, pericardial effusion in 23%, acute neurological deficit in 12% and pulse deficits in 5%.<sup>16</sup>

The chest x-ray reveals mild to moderate mediastinal enlargement, with a prominent aortic silhouette in approximately 85% and a pleural effusion in 12-38% of patients.<sup>3,16</sup> There are no diagnostic features on the ECG and transthoracic echocardiography is of limited value in view of its low sensitivity.<sup>3</sup> Aortography has historically been used to investigate patients with suspected aortic dissection, but does not detect IMH in 87% of patients.<sup>17</sup>

In patients who are clinically stable, MR imaging is the investigation of choice, with a sensitivity and specificity approaching 100%.<sup>18,19</sup> IMH is suggested by the identification of crescentic aortic wall thickening that typically extends superiorly and inferiorly along the aortic wall. There is no evidence of a dissection flap or penetrating aortic atherosclerotic ulcer<sup>20</sup> and the shape of the aortic lumen is preserved. The IMH is of intermediate signal intensity on T1-weighted images in the acute phase and may be difficult to separate from the surrounding aortic wall.<sup>20</sup> On T2-weighted images however, recent haemorrhage appears as an area of high signal intensity. As methaemoglobin accumulates over several days, the signal intensity increases on T1-weighted images and remains high on T2-weighted images. The presence of flow within the haematoma can be assessed using dynamic phase-contrast imaging and time-of-flight gradient-echo pulse sequences.<sup>15,20</sup>

IMH must be differentiated from other causes of aortic wall thickening such as aortitis, atherosclerotic plaque formation and adherent mural thrombus.<sup>14</sup> Thrombus does not typically develop in aneurysms of the ascending aorta because of the high velocity of flow in this region.<sup>21,22</sup> The MR imaging appearances of atherosclerosis include irregular plaques with narrowing of the aortic lumen,<sup>23</sup> as opposed to the crescentic thickening of IMH. Aortitis causes mural thickening that involves segments of the aortic arch and its branch vessels with normal segments between involved sites.<sup>15</sup>

The availability and speed of image acquisition afford CT some advantages over MR, particularly in the critically ill

patient.<sup>14</sup> IMH is defined as a non-enhancing circular or crescentic thickening of the aortic wall without evidence of a typical intimal flap.<sup>1</sup> Fresh haemorrhage appears as high density signal, compared with adjacent aortic layers, and may be associated with inward displacement of intimal calcification.<sup>14</sup> The administration of contrast fails to demonstrate flow within the haematoma. Other causes of periaortic attenuation such as aortic rupture, penetrating ulcer of the aorta and aortitis, are distinguished by the appearances on CT images after the administration of iodine contrast and their clinical presentation.<sup>20</sup> The sensitivity and specificity of CT imaging are high, however a second imaging modality such as MR is occasionally required.<sup>3,8</sup>

In many centres, TOE is utilised as the primary imaging technique. It has advantages in patients who are haemodynamically unstable and allows ready assessment of cardiac anatomy and function. The limitation of TOE is sub-optimal imaging of the aortic arch and great vessels. The typical features of IMH looked for on TOE imaging include crescentic or circular thrombus-like thickening of the aortic wall of at least 5 mm with preservation of a circular lumen.<sup>3,8,9</sup> The absence of an intimal tear or a dissection flap is a prerequisite for the diagnosis.<sup>3</sup> Other echocardiographic features include the absence of flow within the area of wall thickening, the presence of echolucent areas and displacement of intimal calcification.<sup>9</sup> IMH can be difficult to distinguish from a thrombosed false lumen following an aortic dissection or severe atherosclerotic disease. When aortic haematoma is circumferential, a second imaging modality is required to confirm the diagnosis.<sup>24</sup> The sensitivity of TOE for the diagnosis of IMH is reported as 90-100%,<sup>9,25</sup> with a specificity of approximately 90%.<sup>2,9</sup>

There are no randomised trials evaluating the management of IMH. Standard surgical treatment is replacement of the diseased segment of the aorta, whereas medical therapy entails rigorous control of blood pressure with beta blockers and additional antihypertensive drugs.

Surgical therapy for Type A IMH is associated with a 82-100% 30 day survival, in contrast to medical therapy where there is a 20-50% 30 day survival.<sup>3,9,16,26</sup> Patients with Type A IMH treated medically have a high rate of early complications requiring surgical intervention, with progression to overt dissection in 80-100% of patients.<sup>12,15</sup> A small proportion, however, have complete or partial regression of the IMH on serial imaging.<sup>8,27</sup> It has been suggested that patients aged over 80 years with type A IMH should be considered for medical treatment with serial imaging in view of the perceived high operative mortality of surgical treatment.<sup>28</sup>

Patients with Type B IMH fare equally well with medical or surgical therapy.<sup>3</sup> Medical therapy has an observed 30 day survival of 80-96%.<sup>3,16</sup> Approximately 12-20% of patients with Type B IMH develop complications that are either fatal or for which surgery is required in the first six months after presentation.<sup>12,15,29</sup> Approximately a quarter exhibit resolution of the haematoma, however some will subsequently develop either saccular or fusiform aneurysms.<sup>30</sup>

Some debate persists as to whether IMH exists as a separate entity or is a precursor to classic aortic dissection. In some cases, IMH may in fact be dissection in which the intimal flap has been missed or has spontaneously closed. Even with the use of improved imaging techniques, differentiating the two diagnoses can be difficult. Despite the absence of randomised studies, observational series support early surgical management of patients presenting with Type A IMH. In patients with Type B IMH, a medical approach is indicated in the first instance. Regular follow-up



imaging for evidence of intimal disruption, progressive IMH or the development of complications is advisable.

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**Correspondence.** Dr Michael Williams, Department of Cardiology, Dunedin Hospital, 201 Great King Street, Dunedin. Facsimile: (03) 474-7655; Email: michael.williams@stonebow.otago.ac.nz

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## Treatment delays for patients with acute myocardial infarction within the Coromandel region of New Zealand

**Christopher Nunn, Cardiologist, Department of Cardiology, Waikato Hospital, Hamilton; Mathew Scott, Medical Student, Wellington School of Medicine, Wellington; John Lennane, Physician, Department of Medicine, Thames Hospital, Thames.**

### Abstract

**Aim.** To assess treatment delays incurred by Coromandel patients requiring thrombolytic therapy for acute myocardial infarction at Thames Hospital.

**Methods.** A chart search was undertaken at Thames Hospital to identify all patients admitted from July 1993 to July 1998 with a diagnosis of acute myocardial infarction who were treated with thrombolytic therapy. Times of pain onset, general practitioner (GP) assessment, transportation, hospital arrival and thrombolytic administration were noted. Additional information, when required, was obtained from the patient's GP or the St Johns Ambulance service.

**Results.** 153 patients were thrombolysed at Thames Hospital over this period, mean age 65.1 years, 36.6% in heart failure. The mean time from pain onset to GP contact was 157.2 minutes and varied from 63.2 minutes in

Coromandel Township to 272.5 minutes in Pauanui. Delays from GP contact to thrombolysis were longer for patients living in outlying areas versus Thames and its environs,  $169.4 \pm 45.9$  versus  $125.2 \pm 50.4$  minutes (mean  $\pm$  SD) respectively,  $p < 0.001$ . This contributed to a total delay from pain onset to thrombolysis of  $316.7 \pm 145.8$  minutes for patients in outlying areas versus  $269.1 \pm 185.8$  minutes for local patients ( $p = 0.014$ ).

**Conclusions.** Delays in providing thrombolytic therapy for acute infarct patients reflect not only transport times but also delays in seeking initial medical assessment and hospital triage times. Transport times become particularly significant for those outside of Thames and its environs. Only with improved patient education and local delivery of thrombolytic therapy will these delays be adequately addressed.

NZ Med J 2001; 114: 41-3

Thrombolytic therapy has been shown to reduce mortality in patients suffering an acute myocardial infarction (AMI).<sup>1-4</sup> However, the reduction in mortality is markedly attenuated the longer treatment is delayed after onset of infarction.<sup>1-3,5</sup> This delay arises not only from initial patient presentation, but also from subsequent triaging and transportation to a hospital base. In New Zealand, what scant information is available on the extent of these delays is largely confined to tertiary hospitals in urban areas.<sup>6,7</sup>

New Zealand is a rural country with many isolated areas. Patients from these areas are the most disadvantaged but the

least studied. Coromandel is a region covering approximately 500 km<sup>2</sup>, with a population that varies from 20 000 in the winter to over 100 000 in the summer. The population is widely scattered and, as in many parts of New Zealand, many live considerable distances from the nearest medical centre. This region was therefore chosen to assess delay to treatment for patients within a rural area presenting with acute infarction requiring thrombolytic therapy.

The data obtained will provide a baseline when planning a community thrombolytic program which is due to commence in the region.

## Methods

Patients admitted to Thames Hospital with acute myocardial infarction between July 1993 and June 1998 were identified using the hospital's computerized record system. The patient's notes were reviewed to identify those who had an admission diagnosis of myocardial infarction suitable for thrombolytic therapy ie with ST elevation of greater than 1 mm in limb leads or greater than 2 mm in chest leads. Patient demographics were recorded, along with coronary artery risk factors, history of prior ischaemic events, clinical status at admission and length of hospital stay.

Process delays from the time of pain onset to eventual thrombolysis were recorded using a variety of information sources. The hospital records frequently contained incomplete details of times involved and therefore both ambulance records and GP notes were used for supplementation. Specific times were noted for pain onset, ambulance call-out and dispatch, initial medical assessment, departure from the general medical practice, hospital arrival and administration of thrombolysis. In-hospital and six month events recorded were: repeat myocardial infarction, coronary artery bypass surgery, coronary balloon angioplasty, stroke and death. Geographical location of each patient was noted and an arbitrary division made between those areas less than half an hour by road from Thames and those further afield. Areas considered to be a part of Thames and its environs were: Thames township, Paeroa and Ngatea. Towns considered to be greater than half an hour away were: Coromandel Township, Whitianga, Tairua, Pauanui, Waihi Township and Whangamata. Patients living between main population areas were allocated to the nearest town for the purposes of these comparisons. Statistical analysis was undertaken using Chi squared, analysis of Students t test for discrete variables and continuous variables respectively. Non-parametric analysis was undertaken using the Mann-Whitney U Test. Significance was set at a p value of <0.05 (2 tailed). Analyses were done using Statistica version 5. 1. Data are given as mean  $\pm$  SD.

## Results

Over the five year period, there were 264 patients admitted with a diagnosis of acute myocardial infarction. Only 208 were candidates for thrombolysis based on ECG criteria. 54 patients had contraindications to thrombolytic therapy largely related to bleeding concerns. Very few patients were denied thrombolysis because of delayed presentation per se.

A total of 154 patients were admitted to Thames Hospital with an admission diagnosis of acute myocardial infarction and were thrombolysed. The hospital record for one patient could not be located and his results were excluded from further analysis. Treatment times for nine patients were not obtained from any information source and their data were excluded from analyses of treatment delays. Seventeen patients were lost to follow-up, giving an overall follow-up rate at six months of 88.2%.

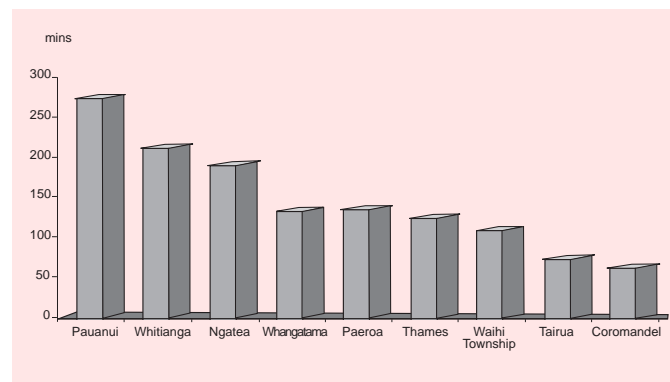
Mean age of the patients was 65.1 years and 77.1% were male (Table 1). This was a high risk population with 36.6% having clinical and/or radiological evidence of cardiac failure on admission. For the analyses of treatment delays, 59 patients (41.0%) came from within the Thames and environs area. Another 77 patients (53.5%) came from those areas greater than half an hour from Thames, but within Coromandel Peninsula itself. The remaining eight patients came from isolated areas within the Hauraki plains and were excluded from the comparative analysis of treatment delays within the Coromandel Peninsula.

**Table 1. Population characteristics.**

Total Number	153
Age (mean)	65.1 yrs
Smokers	49 (32.0%)
Previous MI	32 (20.9%)
Previous CABG	3 (2.0%)
Hypertension	60 (39.2%)
Hyperlipidaemia	95 (62.1%)
Heart Failure (on admission)	56 (36.6%)
Diabetes	16 (10.5%)

MI = Myocardial infarction; CABG = coronary artery bypass graft.

**Treatment delays.** Time delays experienced before patients were seen initially by their GP varied widely between areas (Figure 1). Coromandel had the shortest time to initial assessment, averaging just over one hour, whereas patients from the Pauanui and Whitianga areas were particularly disadvantaged (Figure 1). Elderly patients (>75 years) and those with pain onset out of hours experienced additional delays of 50.8 and 55.4 minutes respectively, before being seen by their GP (Table 2). Subsequent treatment times for the region as a whole revealed an average delay from pain onset to thrombolysis of 5 hours 18 minutes. 47.7% of this delay (2 hours 32 minutes) occurred after the patient had initially been seen by their GP.



**Figure 1. Delays in patient assessment by the GP according to area.**

**Table 2. Delays in initial GP presentation according to time of pain onset and patient age.**

	Time Delay (minutes)	p value
In-Hours (8am-5pm)	118.3 $\pm$ 115.3	
Out of Hours	173.7 $\pm$ 171.7	0.042*
Elderly (>75 yrs)	183.6 $\pm$ 160.3	
Younger Patients ( $\leq$ 75 yrs)	132.8 $\pm$ 141.7	0.082†

\*For In-hours versus Out of hours. †For elderly versus younger patients.

Total delays were reduced for patients from Thames and its environs, compared to those living further afield (Table 3, Figure 2). This largely reflected the difference in travel times and resulted in a net reduction in time from pain onset to thrombolysis of 47.6 minutes for patients living within Thames (269.1  $\pm$  185.8 versus 316.7  $\pm$  145.8 minutes for outliers (p = 0.014)).

**Table 3. Influence of location on all treatment times.**

Treatment period	Areas >1/2 hour from Thames	Thames and Environs	p value
Pain onset to GP assessment	147.3 $\pm$ 136.4	143.8 $\pm$ 169.5	NS
GP assessment	36.6 $\pm$ 17.7	37.7 $\pm$ 40.9	NS
Travel time	72.6 $\pm$ 24.0	28.5 $\pm$ 17.2	<0.001
Hospital delay	60.2 $\pm$ 36.6	59.1 $\pm$ 28.9	NS
Total time: GP contact to thrombolysis	169.4 $\pm$ 45.9	125.2 $\pm$ 50.4	<0.001
Total time: Pain onset to thrombolysis	316.7 $\pm$ 145.8	269 $\pm$ 185.8	0.014

**Events post thrombolysis.** Average duration of hospital stay was 7.2  $\pm$  3.4 days. Acute events at the time of thrombolysis were few, with eight patients requiring defibrillation, one anaphylaxis to streptokinase and five cases of bleeding. There were no in-

hospital strokes. The incidence of in-hospital revascularization was low, and at six months, eight patients had undergone PTCA and four had CABG. In-hospital mortality was 11.1% and climbed to 15.4% at six months.

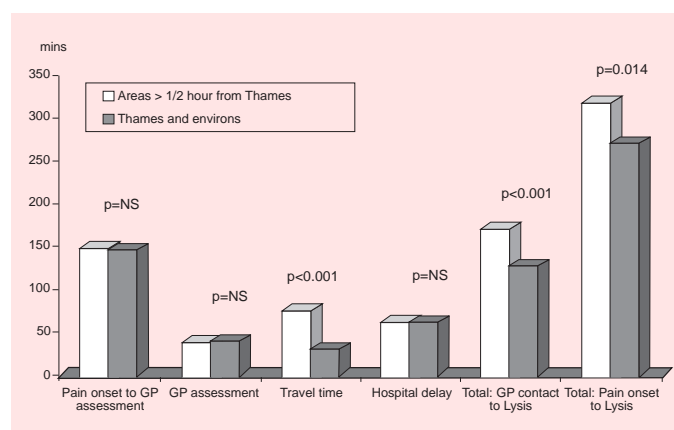


Figure 2. Treatment delays for local Thames patients versus those living more than 1/2 hour away.

## Discussion

Therapies for acute myocardial infarction have evolved rapidly over the past decade, with the principal goal of re-establishing normal coronary flow to the occluded coronary artery.<sup>1-3,8</sup> Whether drugs or mechanical methods are used to obtain reperfusion, the earlier treatment is commenced the greater the benefit.<sup>4,5,9-14</sup> This is particularly so in the early stages of infarction, where it has been shown that up to 60-80 lives per 1000 might be saved per hour of earlier treatment.<sup>15</sup>

This paper describes the experience of patients from a New Zealand rural community who required thrombolytic therapy for acute myocardial infarction. The initial delay in first seeking medical attention averaged 159.3 minutes (median 89 minutes) but varied widely between geographic areas and was particularly prolonged in Whitianga and Pauanui. The additional delays in these areas may at least in part be explained by local geography. In both cases, there are large sub-populations separated from GP services by waterways, necessitating prolonged road travel. Age and pain onset out-of-hours contributed additional delays in seeking medical attention. The extent of these delays is consistent with international experience, and attempts at reducing them with education programs etc. have not always been successful.<sup>14,16-20</sup>

Subsequent delays involved transportation and the process of hospital triaging etc. The latter delay averaged  $60.5 \pm 35.3$  minutes and is consistent with overseas experience with reports of between 45 and 90 minutes.<sup>6,7,18,19,21-23</sup> A recent New Zealand study found that despite specifically focused staff training, door to needle times could only be reduced from 66 minutes to 52 minutes when thrombolysis was administered in the coronary care unit.<sup>6</sup>

For outlying patients, once initial medical assessment had been sought,  $169.4 \pm 45.9$  minutes lapsed before thrombolytic therapy was given. This comprised 53.5% of the total delay from pain onset to treatment. Indeed, it was this transport delay that accounted for the difference in treatment times between outlying areas and Thames itself.

In order to provide timely delivery of thrombolytic therapy, each of these delays must be addressed individually. Patient education and provision of appropriate medical services to isolated communities would help to improve the initial delay in seeking medical assistance.

Community thrombolysis is another critical step in reducing both transport and hospital triage delays. A recent review of treatment delays in northeast Scotland found that once medical

attention had been sought there was a median delay of another 150 minutes before thrombolytic therapy was given in hospital.<sup>23</sup> This was reduced to 45 minutes if thrombolysis was given by the GP, which was even less than the 58 minute delay experienced by patients within the immediate city environs who were admitted directly to coronary care for thrombolysis.

This review is limited by the patient selection process and the fact that it is retrospective and required information from multiple sources. The selection process was dependent on the coding of patients following discharge which did not necessarily reflect admission diagnosis. The details of patients admitted with a diagnosis of acute myocardial infarction and not thrombolysed were not recorded. Most of these either did not achieve ECG criteria for thrombolysis or had contraindications to thrombolytic therapy because of bleeding concerns.

A few patients would not have received thrombolysis because of delayed presentation - which would have the potential to increase the treatment delays recorded here. The extent of this increase, however, is likely to be small in view of the few patients involved and only serves to reinforce the delays experienced by patient in rural communities. Efforts should be made to address these delays through patient education and community thrombolysis.

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**Correspondence.** Dr Chris Nunn, Department of Cardiology, Waikato Hospital, Private Bag, Hamilton. Fax: (07) 839 8760.

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# Outcome following heart transplantation in Maori and Polynesian patients: a comparison with European New Zealanders

RD Costa, Medical Student, Monash University, Melbourne; PN Ruygrok, Cardiologist; HA Coverdale, Cardiologist; TM Agnew, Cardiologist; HC Gibbs, Recipient Coordinator; D Reddy, Recipient Coordinator; DA Haydock, Cardiothoracic surgeon; AR Kerr Cardiothoracic surgeon; RML Whitlock, Biostatistician, Green Lane Hospital, Auckland.

## Abstract

**Aim.** To compare demographic, clinical and outcome data of Maori and Polynesian with New Zealand European heart transplant patients.

**Methods.** A retrospective analysis was made of data from the 104 patients who underwent heart transplantation at Green Lane Hospital over a period of twelve years, of whom 79 were European, 23 Maori/Polynesian, and two Asian. Clinical characteristics, blood group, HLA matching and outcomes of recipients were compared.

**Results.** There was no significant difference in age and gender between the two groups. Maori and Polynesian patients were heavier, had a greater body mass index and

were more likely to have rheumatic heart disease than their European counterparts. Maori/Polynesian patients were predominantly blood group A, whilst European patients were mainly group O. The waiting time for a donor heart was similar in both groups. There was no significant difference in number of rejection episodes and survival.

**Conclusions.** Green Lane Hospital has the largest international experience of heart transplantation in Maori and Polynesian patients. Although there are some differences in clinical profile, outcome in terms of rejection episodes and survival is similar in the two groups.

NZ Med J 2001; 114: 44-6

New Zealand has a population of 3.8 million people and, with 740 000 of Maori and Polynesian descent, has the largest number of inhabitants of these peoples of any country in the world. It is probable that Green Lane Hospital has the largest experience of heart transplantation in people of Maori and Polynesian ancestry. We sought to characterise this group of patients and compare their outcomes with those of European descent.

## Methods

A retrospective analysis was carried out on all patients who underwent cardiac transplantation at Green Lane Hospital, Auckland, from the time of the first transplant in December 1987 until June 1999. The ethnic origin of the recipients was determined from that stated on the hospital registration form. Demographic details, clinical information and outcomes of the Maori and Polynesian recipient population were compared to their 'New Zealand European' counterparts.

Recipients were allocated donor organs on the basis of red blood cell ABO compatibility, body weight and urgency. Prior to transplantation, a direct lymphocytic cross match was performed and was negative in all cases. Human lymphocyte antigen (HLA) typing for class I and II antigens was performed preoperatively (A, B, DR) on all recipients and donors, but no attempt at matching was undertaken. Organ retrieval and implantation methods were similar to those previously described.<sup>1</sup> Following orthotopic transplantation, patients were transferred to the intensive care unit and, when stable, to the surgical ward. Immunosuppression was achieved with cyclosporin, prednisone and azathioprine. In the first 98 patients, equine anti-thymocyte globulin was administered until therapeutic levels of cyclosporin were achieved, and in the last five patients, induction therapy was withheld and patients were randomised to receive azathioprine or sirolimus according to a multicentre study protocol. Diltiazem, aspirin, and in recent years, pravastatin were introduced in the post-operative period and endomyocardial biopsies performed with diminishing frequency from weekly for the first month, until one year after transplantation, after which surveillance biopsies were usually no longer performed. Following transplantation, the number of episodes of significant rejection in the first year, defined as Grade 3A or greater according to the International Society for Heart and Lung Transplantation classification,<sup>2</sup> and survival for both the Maori/Polynesian and European groups, were compared and the causes of death identified.

Categorical variables were compared by Chi squared and Fisher's exact tests. Continuous differences were tested using a Mann-Whitney U test. Five-year actuarial curves were constructed using the Kaplan-Meier method<sup>3</sup> and comparisons between groups were made by the log-rank method, with the end-point being death of any cause. A p value of  $\leq 0.05$  was considered to be significant.

## Results

Over the twelve-year study period, 104 patients underwent cardiac transplantation at Green Lane Hospital. 23 were of Maori (18) and Polynesian descent (Samoan - 2, Nuicuan - 2, Cook Islander - 1), 79 of European and 2 of Asian ancestry. The proportion of Maori and Polynesian patients represented in our transplant population (22%) is similar to that in the New Zealand population (18%). Demographic and clinical data are displayed in Table 1. The recipient groups were similar in terms of age and gender, while their ABO blood groups differed significantly ( $p=0.001$ ). The number of donor and recipient HLA matches were similar in both groups (Table 2). The Maori and Polynesian group had a significantly higher mean body weight ( $p=0.002$ ), and a greater body mass index ( $p=0.002$ ) than European recipients.

When considering the aetiology of native heart disease before transplantation, European patients suffered more from coronary artery disease (35% versus 17%) and congenital heart disease (5% versus 0%) than did Maori/Polynesian recipients, whereas rheumatic heart disease occurred predominantly in the latter group (22% versus 0%). The incidence of dilated cardiomyopathy was the same in both groups. Similar proportions of patients had previously undergone cardiac surgery. The two groups had a similar mean waiting time for transplantation. Although cytomegalovirus (CMV) seropositivity was higher in the Maori/Polynesian group, this was not statistically significant. The hepatitis serology was significantly different between the groups, although in the case of hepatitis B antibody, this finding could be confounded by past immunisation. The number of patients who were hepatitis B surface antigen positive was small.

Over the follow-up period, 21 deaths occurred in the European group (27%) and six in the Maori/Polynesian group (26%). The one and five year survivals were 83% and 76% for Maori/Polynesian patients and 87% and 73% for New Zealand European patients respectively (Figure 1). This difference was not statistically different ( $p=0.98$ ). Beyond five years, when there were three deaths in the European group and one in the Maori/Polynesian group, comparison is less meaningful due to the small numbers.



**Table 1. Demographic and clinical characteristics of the recipient population classified by ethnicity.**

		European	Maori and Polynesian	p value
Number		79	23	
Age (years)	Mean	42.7	38.3	NS
	Range	12-59	14-56	
Gender	Male	68 (86%)	19 (83%)	NS
	Female	11 (14%)	4 (17%)	
Mean weight (kg)		68.6±/-14.1	79.7±/-12.8	0.002
Body mass index		23.0±/-3.3	26.0±/-3.8	0.002
Indication for transplantation	Coronary artery disease	28 (35%)	4 (17%)	
	Cardiomyopathy	44 (56%)	13 (57%)	
	Valvular heart disease	3 (4%)	1 (4%)	
	Congenital heart disease	4 (5%)	0	
	Rheumatic heart disease	0	5 (22%)	0.001
Time on waiting list (days)		133.7	134.5	NS
Pre-operative serology	Antibodies to CMV	39 (49%)	16 (70%)	NS
	HepBsAg positive	1 (1%)	2 (9%)	0.048
	Antibodies to Hepatitis B	13 (16%)	7 (39%)	0.019
Previous cardiac operations		28 (35%)	10 (44%)	NS

CMV = cytomegalovirus. HepBsAg = hepatitis B surface antigen.

**Table 2. Recipient blood group and donor - recipient HLA matching.**

		European	Maori/Polynesian	p value
Blood group	O	45 (57%)	5 (22%)	
	A	28 (35%)	15 (65%)	
	B	6 (8%)	2 (9%)	
	AB	0	1 (4%)	0.001
HLA number of matches	0	14 (18%)	6 (26%)	
	1	31 (39%)	11 (48%)	
	2	24 (30%)	5 (22%)	
	3	7 (9%)	1 (4%)	
	≥4	3 (4%)	0	0.454

**CARDIAC TRANSPLANTS GREEN LANE 1987-99**

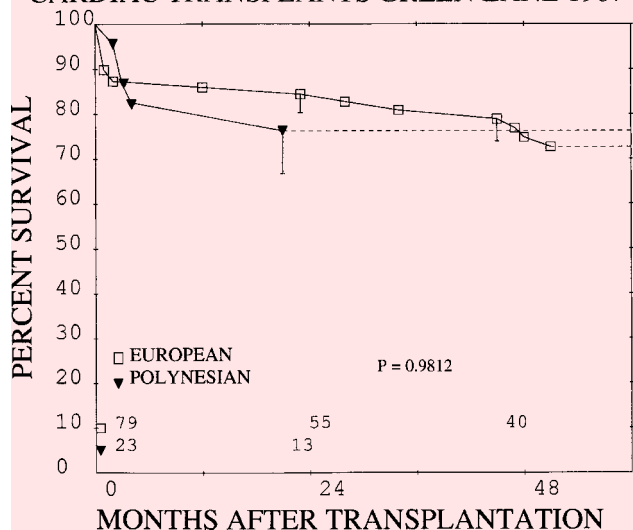


Figure 1. Actuarial survival for Maori/Polynesian and New Zealand European patients. After a death in the Maori/Polynesian group 20 months post-transplantation, there were no further events. The statistical comparison of the groups thus uses an extrapolated value (dotted line) over two-thirds of the five-year period.

There was no significant difference in the number of episodes of rejection in the first three months following transplantation when the two groups were compared, with a mean of 1.04 episodes per patient in both groups.

## Discussion

We have previously reported the outcome following heart transplantation in our unit.<sup>4</sup> As our population has a unique mix of New Zealand Maori/Polynesian and European patients, we sought to identify any differences between the two groups. The one and five year survival rates after cardiac transplantation were 87% and 73% for New Zealand Europeans, and 83% and 76% for Maori/Polynesians respectively. These figures compare favourably to the international experience of 79% and 65%.<sup>5</sup> Survival was not significantly different between Maori/Polynesian and European recipients, however the limitations of the statistical method and the small numbers of Maori/Polynesian patients with long-term follow-up must be considered. After a death in the Maori/Polynesian group at 20 months post-transplantation, there were no further events in the five-year follow-up period. The statistical comparison of the groups thus uses an extrapolated value over two-thirds of the five-year period.

The literature on race and outcome survival after transplantation is concerned largely with black and white American populations, and its applicability to other multiracial societies, such as ours, is doubtful. Being of black race has been identified as a risk factor for death<sup>6</sup> and recurrent rejection following cardiac transplantation.<sup>7</sup> Black recipients have also been found to be more likely to suffer a rejection episode with haemodynamic compromise, with a significant reduction in three-month survival.<sup>8</sup> It has been suggested that greater graft HLA mismatch between donors and black recipients,<sup>9-11</sup> might, in part, account for this. Others have found however, that there was no significant difference in HLA mismatch between white and black Americans.<sup>12</sup> Even when HLA matching was enhanced, there was no significant improvement in survival of black recipients,<sup>11</sup> suggesting that environmental factors may be as important as genetic in determining post-transplant outcome. We do not match for HLA, and retrospectively found a similar degree of mismatch when transplanting predominantly European donor hearts into Maori and Polynesian patients, with a similar mean number of rejection episodes for both groups. Recipient black race has also been identified as a risk factor for the early development of post-transplant coronary disease.<sup>13</sup>

A significant difference in ABO blood group profile between blood donors of Maori and European descent has previously been reported.<sup>14</sup> This is shown in our study in

which the predominant blood group in Maori and Polynesian patients is A and in New Zealand Europeans, O.

The aetiology of end-stage cardiac disease was predominantly dilated cardiomyopathy in both the Maori/Polynesian and European patient groups, with valvular and rheumatic heart disease being the next most common cause in the former, compared to ischaemic cardiomyopathy in the latter group. Similar observations were made when black and white American heart transplant recipients were compared.<sup>11</sup> Our Maori and Polynesian recipients were heavier and their BMI was greater than their European counterparts. We have previously reported the demographic profile of heart donors in New Zealand and found that only 5% were of Maori and Polynesian descent.<sup>15</sup> This has significant implications when matching predominantly European donors with potential Maori/Polynesian recipients whom we have found to differ in both blood group and weight.

A limitation of our study is the differentiation of our patients into two discrete groups. This was done according to the racial group nominated by the patient rather than a more rigid genetic definition. This raises the question of the value of grouping patients according to race in studies such as ours. It is unclear whether the classification of patients into definable discrete races is justifiable or even possible, and the evidence for influence on disease is uncertain.<sup>16</sup> On the other hand, explaining disease outcome differences between races on the basis of socio-economic differences alone is also largely unsubstantiated. The relationships between race, socio-economic status, health and disease are complex.

**Correspondence.** Peter Ruygrok, Cardiology Department, Green Lane Hospital, Green Lane West, Epsom, Auckland. Fax: (09) 630 9906; email: PRuygrok@ahsl.co.nz

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## Memories from 1949

At this general election on November 30, the National Party was returned with the substantial majority of 46 seats to Labour's 34, the latter figure including all the 4 Maori seats. The Labour government's fourteen years of office thus came to an end, and Mr SG Holland has assumed office as prime minister. The new minister of social security and health is Mr JT Watts, of Christchurch, a barrister and solicitor about 40 years of age with a distinguished academic record, who entered parliament six years ago.

The National Party's election policy emphasised prevention and research, and promised a complete reorganisation of the hospital system on a basis of regional control and decentralisation. It supported recent Acts for the more economical management of medical and pharmaceutical benefits, and promised help for the elderly, for the Post Graduate Women's Teaching Hospital in Auckland, and for a number of other projects. With recent and forthcoming appointments inside the health department – notably that of the new director-general, Dr J Cairney – the field is open for much-needed progressive development.

*Lancet* 1949; 2: 1237.

The product licence for cisapride (Prepulsid), a drug used to treat gastric and digestive disorders in adults and children, has been suspended by the Medicines Control Agency after five deaths in the United Kingdom and 125 deaths worldwide that are thought to be associated with the drug.

When the Committee on Safety of Medicines recently reviewed the drug, which is made by Janssen-Cilag, it found rare but serious disturbances in heart rhythm associated with it. Since 1988, when cisapride was licensed in the United Kingdom, the yellow card scheme – under which doctors report adverse drug reactions – has received 60 reports of serious cardiovascular reactions, five of which were fatal.

Worldwide, there have been 386 reports of serious ventricular arrhythmias (125 of which were fatal) suspected to be due to cisapride and 50 reports of sudden unexplained death. Risk factors predisposing a patient taking cisapride to heart rhythm disturbances, such as interacting medicines, could be identified in many, but not all, cases.

*Annabel Ferriman. BMJ* 2000; 321: 259.

Drug companies are using legal loopholes to extend patents for their most lucrative brand name products and delay the entry of cheaper generics on to the market, according to a report from the National Institute for Health Care Management.

Intellectual property protections enacted over the past two decades have increased the average patent life of new drugs by at least 50%, according to the report. Although patent protections were intended to provide incentives for innovation, they have brought higher prices for consumers and hefty profits for brand name makers. Brand name drugs now have patent lives averaging 14-15 years, compared with eight years in the early 1980s.

The report charges that drug companies have used legal loopholes to extend the active life of patents covering their most lucrative drugs, thus keeping cheaper generics out of the market.

*S Gottlieb. BMJ* 2000; 321: 320.

**William A Denny, Professor and Director, Auckland Cancer Society Research Centre, Faculty of Medical and Health Sciences, The University of Auckland, Auckland.**

NZ Med J 2001; 114: 47-8

Over the last 20 years, there have been steady increases in the overall five-year survival rates from cancer,<sup>1</sup> and improving drug treatment has made an important contribution to these. However, cancer chemotherapy is still based primarily on anti-proliferative drugs that selectively kill dividing cells by inhibiting DNA synthesis, replication or processing. This approach resulted from the early concept that cancer cells share a common gross property of uncontrolled growth and division, whereas most normal cells are not rapidly dividing. However, such drugs have a fundamental limitation in that they do not target the basic changes that define a cancer cell, but rather later consequences, and are primarily 'dividing cell specific' rather than 'cancer cell specific'. The collateral damage they therefore cause to rapidly dividing normal cell populations in the body will always limit their effectiveness. While there is still important work to be done to improve drugs of this type (particularly in overcoming their susceptibility to resistance), further quantum jumps in the efficacy of cancer chemotherapy will require new approaches.

### Protein tyrosine kinases

One such new approach is drugs aimed at enzymes that comprise the signalling pathways in cells. Unravelling these complex pathways has been one of the major recent achievements of biomedical research, and this knowledge is now forming the basis for a new wave of anticancer agents.<sup>2</sup> The signalling pathways that control cell division begin at the cell surface with membrane-spanning receptor proteins. Small polypeptide growth factors, that cannot themselves cross the cell membrane, transmit a growth signal to cells by interacting with the accessible extra-cellular region of their particular receptor.

One of the most important classes of such receptors is a small family of proteins known as the erbB family. Two members of this family are of particular interest; the epidermal growth factor receptor and HER2/*neu*.<sup>3</sup> When the appropriate growth factors (epidermal growth factor and heregulins respectively) bind to their extra-cellular regions, these receptors dimerize on the cell surface. This juxtaposes their intra-cellular regions, allowing each one to mutually phosphorylate a number of tyrosine aminoacids on the other by transferring a phosphate group from the associated cofactor adenosine triphosphate (ATP) to the phenol group of the tyrosine (Figure 1). Enzymes capable of carrying out such phosphorylations are called kinases, and this class of enzymes are referred to as protein or receptor tyrosine kinases. This mutual 'autophosphorylation' then changes the shape of the intra-cellular region of the enzyme, allowing a number of other substrate proteins to bind to the active (kinase) site. These are then also phosphorylated and become activated. This is the first step in a chain of such protein phosphorylation events that end up in the nucleus, turning on genes that initiate cell division.

There is much evidence that over-expression of these receptor enzymes is important in cancer development and prognosis. One or other of these enzymes, and sometimes both, are over-expressed in a wide variety of human cancers, especially breast, head-and-neck and ovarian cancer.<sup>4</sup>

Furthermore, such over-expression is associated with poor prognosis, and has been used as a predictive test for this.<sup>5</sup> An ability to shut off this enhanced signalling through these enzymes is therefore of interest as a potential new cancer therapy, and much work has recently been devoted to the development of drugs that can do this. These fall into two main classes, depending on where they exert their action.

### Drugs acting at the extra-cellular growth factor binding region

These compounds (antagonists) bind tightly to the external site usually occupied by the growth factor, but do not trigger the subsequent intra-cellular response (Figure 1). The most useful class are monoclonal antibodies, pure proteins that make multiple contacts with the growth factor binding site. The best known of these antibodies is herceptin (trastuzumab), which is in Phase II trials for metastatic breast cancer, both as a single agent and in combination with cytotoxic drugs.<sup>6</sup>

### Drugs acting at the intra-cellular kinase region

These compounds can bind at either the substrate protein site or the cofactor (ATP) site of the intra-cellular kinase region (Figure 1). Unlike the antagonists, they must be small molecules capable of getting into cells. Early studies favoured targeting the substrate protein site, because this varies greatly in structure between different enzymes. This therefore seemed the best approach to potent drugs that would still be highly selective. In contrast, ATP is a common cofactor for all kinase enzymes, and the structure of its binding site is therefore relatively similar between different enzymes. ATP is also present in high (millimolar) concentration inside cells.

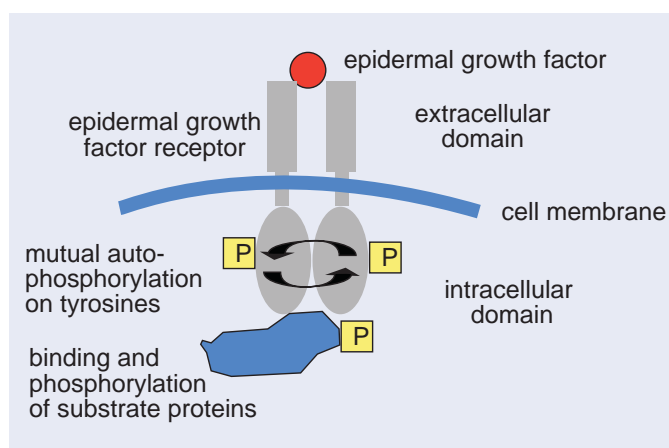


Figure 1. Signalling by extra-cellular epidermal growth factor via binding to its receptor and induction of autophosphorylation, initiating receptor phosphorylation of intra-cellular signalling proteins on tyrosine.

Despite the logic of this approach, potent and selective inhibitors that bound at the substrate protein site proved elusive. The first major step forward in this field was the

near-simultaneous discovery by three groups, at Zeneca, Ciba-Geigy and Parke-Davis, that compounds known as anilinoquinazolines were potent and selective inhibitors, despite binding at the ATP site.<sup>2,3</sup> Independent drug development programmes from these initial leads resulted in two drugs of quite similar overall structure that are currently in clinical trial (Figure 2).

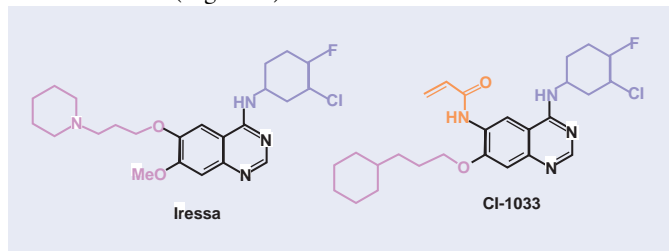


Figure 2. Structures of the reversible (Iressa) and irreversible (CI-1033) small-molecule inhibitors of the epidermal growth factor receptor, indicating the functions of various domains of the drugs. The quinazoline ring (black) binds at the general ATP site; the phenyl ring (blue) fits into an adjacent unique binding pocket; the other side chains (magenta) do not bind to the enzyme but project into space and provide solubility; the acrylamide (CI-1033; red) reacts irreversibly with a unique cysteine residue.

The Zeneca compound Iressa binds reversibly to the ATP site of the enzyme, while the Parke-Davis compound CI-1033 binds irreversibly at the same site through reaction with a cysteine amino-acid.<sup>7</sup> Development of the Parke-Davis compound was carried out jointly by Parke-Davis in Ann Arbor, USA, and the Auckland Cancer Society Research Centre at the University of Auckland. The perceived advantages of an irreversible over a reversible inhibitor are longer-lived inhibition of the enzyme by the former, resulting in a more potent compound that can be given less frequently. The structural similarities between these independently developed compounds suggested a common way of binding to the enzyme, and this was supported by structural studies.<sup>8</sup> In this model, the quinazoline ring (Figure 2; black) binds at the ATP site and the phenyl ring (Figure 2; blue) fits into an adjacent pocket that occurs only in this class of enzymes, conferring the selective binding. The other side chain (Figure 2; magenta) does not bind, but projects into space and provides water-solubility. The acrylamide on CI-1033 (Figure 2; red) reacts

irreversibly with a cysteine amino acid that occurs only in these enzymes.

Recent reports from the 2000 Annual meetings of both the American Association of Cancer Research and the American Association for Clinical Oncology suggest that the reversible inhibitor Iressa given orally is non-toxic and shows some clinical activity as a single agent.<sup>9,10</sup> Furthermore, like the monoclonal antibodies, this activity is potentiated in combination with cytotoxic drugs.<sup>11</sup> No results from the CI-1033 trials have been reported so far.

## Conclusions

The inhibitors of the erbB family of receptors discussed here represent a new class of non-cytotoxic anticancer drugs, rationally designed to interrupt growth signalling pathways that are specifically activated in cancer cells. Early clinical results suggest that this general class of compounds may play an important future role in cancer chemotherapy, especially in combination with cytotoxic drugs.

**Correspondence.** Professor Bill Denny, Auckland Cancer Society Research Centre, Faculty of Medical and Health Sciences, The University of Auckland, Private Bag 92019, Auckland. Fax: (09) 373 7502; Email: b.denny@auckland.ac.nz

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