Design Features and Baseline Characteristics of the LIPID (Long-Term Intervention With Pravastatin in Ischemic Disease) Study: A Randomized Trial in Patients With Previous Acute Myocardial Infarction and/or Unstable Angina Pectoris

The LIPID Study Group*

LIPID is a multicenter, double-blind, randomized, placebo-controlled trial comparing the effects of pravastatin, 40 mg/day, with placebo, given for ≥5 years, in patients aged 31 to 75 years with a total cholesterol level at baseline of 4.0 to 7.0 mmol/L (155 to 270 mg/dl), and with a history of acute myocardial infarction (AMI) or hospitalization for unstable angina pectoris (UAP). Each group receives dietary advice according to National Heart Foundation guidelines. Individual care of each patient is otherwise left to the discretion of the patient's usual doctor. The study has a primary outcome of coronary mortality, and is designed to detect an 18% reduction with 80% power. From April 1990 to September 1992, 11,106 patients were registered, and following the run-in phase, 9,014 were randomized: 5,754 (64%) after a qualifying event of AMI and 3,260 (36%) after hospitalization for UAP. The randomized population includes relatively large numbers in subgroups not assessed reliably in earlier trials: 1,511 women, 3,516 patients aged ≥65 years, 777 diabetics, and 3,829 patients with serum cholesterol <5.5 mmol/L (213 mg/dl) at baseline. With a projected 700 fatal coronary events, the trial should be able to detect important reductions in coronary mortality and contribute substantially to prospective meta-analyses to detect effects on total mortality. The spectrum of patients being assessed will improve the reliability of evidence for the benefits and risks of cholesterol-lowering therapies in patients with lower cholesterol levels and in other important subgroups.

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At the time at which the LIPID (Long-Term Intervention with Pravastatin in Ischemic Disease) study was designed, meta-analyses of randomized trials of cholesterol-lowering therapies had confirmed a reduction in coronary artery disease (CAD) morbidity in both primary and secondary prevention, and suggested a small reduction in CAD mortality. The effect on total mortality was uncertain from these trials, which often tested modest cholesterol reductions for a relatively short duration.[1–9] The advent of more powerful cholesterol-lowering drugs, particularly the hydroxymethylglutaryl coenzyme A reductase inhibitors, has allowed the effect of larger cholesterol reductions on both coronary and total mortality to be evaluated in individual trials.[10–11] The LIPID study was designed to test the effects of cholesterol reduction with pravastatin on coronary mortality in patients with preexisting CAD, and particularly with cholesterol levels in a range similar to that found in clinical practice, including a large number with average or below-average levels.

METHODS

Study aims: The primary objective of LIPID is to investigate whether treatment with pravastatin in patients with a history of acute myocardial infarction (AMI) or hospitalization for unstable angina pectoris (UAP) and a baseline cholesterol in the range 4.0 to 7.0 mmol/L (155 to 270 mg/dl), will reduce coronary mortality over a period of ≥5 years. Secondary objectives are to determine the effect of treatment on (1) total mortality; (2) the incidence of AMI (fatal and nonfatal); (3) total days of hospitalization; and (4) serum lipid fractions, and the relationship of changes in them to changes in CAD mortality.

Study design and eligibility: Patients aged 31 to 75 years who either had an AMI or were hospitalized for UAP within the previous 3 months to 3 years, and gave written informed consent, were registered. Major exclusion criteria included a significant medical or surgical event in the last 3 months, unavailability for long-term follow-up, significant cardiac failure (New York Heart Association class III or IV), renal or hepatic disease, uncontrolled endocrine disease, and treatment with other lipid-lowering agents, cyclosporin, or investigational drugs. After registration, patients entered a single-blind, run-in phase of at least 8 weeks, during which time they were given placebo and appropriate dietary advice. Patients with fasting total serum cholesterol in the range of 4.0 to 7.0 mmol/L (155 to 270 mg/dl) and a serum tri-

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*A complete listing of LIPID investigators is given in the Appendix.

glyceride ≤5.0 mmol/L (445 mg/dl) measured centrally after 4 weeks were eligible. If, after the run-in phase, they were still agreeable to be randomized and had demonstrated at least 80% compliance with study medication, and their usual doctors were uncertain of the long-term benefits of cholesterol lowering for them, they were randomized to receive pravastatin or placebo. A randomized block design was employed, with stratification according to diagnosis of either AMI or UAP, with the plan to recruit two thirds of the cohort with AMI and one third with UAP only. Approval was obtained from the relevant ethics committee for each participating center.

Treatment, monitoring, and patient management: Patients receive 40 mg (two 20 mg tablets) pravastatin or matching placebo, taken in the evening, and all receive dietary advice with the aim of reducing fat intake to <30% of total energy intake and dietary cholesterol to <300 mg/day. All lipid assays (total cholesterol, high-density lipoprotein [HDL], triglycerides and calculated values of low-density lipoprotein [LDL]) are performed at a central lipid laboratory. The LIPID study is a pragmatic trial,[12] in which the patient's usual care is at the discretion of the patient's own doctor. This allows changes in lipid treatment to be made in the light of local cholesterol results. A patient review, including serum alanine transaminase measurement, occurs every 6 months. Fasting samples for lipid assays are collected at 6 months and yearly after randomization. It is recommended that treatment be suspended if there is significant elevation of serum alanine transaminase (>3× upper limit of normal) or unexplained muscle pain and elevated serum creatine kinase (>4× upper limit of normal). Based on central lipid assays, for persistently low total cholesterol <3 mmol/L dose reduction or cessation of study medication is recommended; for persistent elevation ≥7.5 mmol/L, the investigator is advised to consider additional dietary measures initially, and if these are insufficient, other lipid-lowering therapy.

Study outcomes: All deaths and AMI are reviewed by the outcome assessment committee; such review is based on documentation from hospital records, death certificates, autopsy reports, and physician's notes. The committee is blinded to treatment and cholesterol level results. The primary study outcome, coronary mortality, is further classified as due to fatal AMI, sudden cardiac death, death in hospital after possible AMI, heart failure or other coronary cause. The secondary outcome, definite AMI, is defined by development of new pathologic Q waves in at least 2 related electrocardiographic leads, or any 2 of the following 3 criteria: typical ischemic pain for ≥15 minutes; elevated serum creatine kinase greater than twice normal; evolutionary ST-T wave changes (ST elevation ≥2 mm in anterior leads, ≥1 mm in inferior or lateral leads; followed by development of inverted T waves ≥1 mm) over at least 1 day in ≥2 related leads.

Statistical considerations: The trial was originally designed to recruit 7,000 patients, based on assumptions that pravastatin would lower total cholesterol by 25% compared with placebo, but that a smaller average difference of about 18% would occur in the trial because of reduced compliance leading to discontinuation of study medication (drop-outs) or commencement of other lipid-lowering treatment in those taking placebo (drop-ins). Consequently, a reduction in CAD mortality of approximately 18% would be plausible. It was anticipated that 80% of all deaths would be due to CAD, occurring at a rate of approximately 2%/annum after the first year, based, in part, on survival data from an Australian register of postinfarct patients.[13] The original sample size of 7,000 was therefore planned to detect an 18.4% reduction in CAD mortality with 80% power by using a 2-sided, 5% alpha level test, and a comparison of cumulative proportions.[14] This corresponded to a total of approximately 700 CAD deaths.

TABLE I Reasons for Exclusion of the 2,092 Patients Registered but not Randomized for the LIPID Study*

Reason Not Randomized	Number (% reg.)
Lipids out of range	926 (8.3)
Cholesterol >7.0 mmol/L (>270 mg/dL)	707 (6.4)
Cholesterol <4.0 mmol/L (<154 mg/dL)	123 (1.1)
Triglycerides >5.0 mmol/L (>442 mg/dL)	96 (0.9)
Ineligible due to:	480 (4.3)
Ischemic event within 3 months	161 (1.4)
Surgery/major illness within 3 months	105 (0.9)
Other treatment†	42 (0.4)
Abnormal liver function	107 (1.0)
Other laboratory abnormalities	91 (0.8)
Total ineligible	1,333 (12.0)
Patient discontinued	759 (6.8)
Patient decision	650 (5.9)
Doctor decision	92 (0.8)
Not specified	17 (0.2)
Total exclusions	2,092 (18.8)

*Total registered = 11,106. For patients with >1 reason for ineligibility, all known reasons are given.
†Other treatment: investigational drug, lipid-lowering therapy, cyclosporin.
LIPID = Long-Term Intervention with Pravastatin in Ischemic Disease; reg. = registered.

Due to uncertainty in the original assumptions, it was planned to review them after 1 year while recruitment was still in progress. At this time, the assumptions concerning compliance, qualifying diagnosis, drop-ins and drop-outs were approximately correct or conservative. However, the CAD death rate and difference in total serum cholesterol levels were both less than anticipated. To correct for this, the sample size was increased to approximately 9,000 patients by extending the recruitment phase. The final sample size of 9,014 patients with follow-up until there are 700 CAD deaths gives the trial 80% power to detect an 18.3% difference in 5-year CAD mortality, using a log rank test.[15] The protocol allows for extended follow-up until this number of end points has been reached.

Interim analyses: An independent safety and data monitoring committee meets at least every 6 months. Three formal interim analyses have been planned at approximately 2, 3, and 4 years after the end of recruitment to examine differences in total mortality or significant increases in serious adverse events associated with pravastatin treatment. If there should be a difference of ≥3 SDs ($p < 0.003$) for any one of these outcomes, the safety and data monitoring committee would advise the management committee.

TABLE II Baseline Characteristics of 9,014 Patients Randomized to Pravastatin or Placebo

Baseline Characteristics and History	Number (%)
Age (yr)	
<40	106 (1)
40–44	303 (3)
45–49	640 (7)
50–54	1,038 (11)
55–59	1,371 (15)
60–64	2,040 (23)
65–69	2,170 (24)
≥70	1,346 (15)
Male	7,503 (83)
Female	1,511 (17)
Qualifying event	
UAP	3,260 (36)
AMI	5,754 (64)
Years since qualifying event*	1.0 (0.5, 1.9)
Risk factors	
Current smoker	869 (10)
Ex-smoker	5,737 (64)
History of systemic hypertension	3,728 (41)
Diabetes mellitus	777 (9)
Obesity (body mass index >30)	1,126 (13)
Other cardiovascular disease	
Claudication	904 (10)
Stroke	363 (4)
Transient ischemic attack	324 (4)
Angina grade (CCVS)	
No angina	5,686 (63)
No limitation (I)	2,580 (29)
Slight limitation (II)	673 (7)
Marked limitation (III)/at rest (IV)	75 (1)
Dyspnea grade (New York Heart Association)	
No dyspnea/no limitation (I)	8,156 (90)
Dyspnea on normal exertion (II)	851 (10)
Dyspnea on mild exertion (III)	7 (0.1)
Other treatment	
Aspirin	7,343 (82)
Beta blocker	4,209 (47)
Calcium antagonist	3,093 (34)
Angiotensin-converting enzyme inhibitor	1,418 (16)
Nitrates	2,623 (29)
Coronary revascularization	
Angioplasty only	988 (11)
Coronary bypass only	2,430 (27)
Both angioplasty and bypass	272 (3)

*Median (25th, 75th percentile).
AMI = acute myocardial infarction; CCVS = Canadian Cardiovascular Society; UAP = unstable angina pectoris.

Substudies: The LIPID study incorporates several important substudies examining cost-effectiveness (including quality of life), diet, psychological well being, and carotid ultrasound, by using representative samples of approximately 500 to 1,000 patients of the LIPID study population. Each substudy is reviewed by a related studies subcommittee to ensure it is well designed to answer the ancillary questions efficiently and without compromising the main study.

RESULTS

Recruitment: The first patient was recruited in April 1990. Randomizations occurred from June, 1990, until December, 1992. Of the 11,106 patients registered, 9,014 were randomized: 5,958 from Australia and 3,056 from New Zealand, from a total of 87 centers. For the 2,092 patients (18.8%) registered but not randomized, 12.0% were ineligible and 6.8% discontinued. The main reason for exclusion was a total cholesterol >7.0 mmol/L, occurring in 707 patients (6.4%) (Table I). Run-in was extended an extra 4 weeks in 1,046 patients, in whom initial lipid levels were out of range. With further dietary measures, 473 of these patients were able to be randomized.

Baseline characteristics: Selected baseline characteristics of randomized patients are shown in Tables II and III. Over 3,500 (39%) patients are ≥65 years of age and 1,511 (17%) are female. The qualifying event was hospitalization for UAP in 3,260 patients (36%) and AMI in 5,754 (64%); 1,144 (13%) who qualified with AMI also had a history of UAP; 74% have smoked, but most (51%) had stopped for at least 1 year; 777 (9%) had diabetes mellitus of whom 109 (14%) were insulin-dependent. Over 15% had a history of other cardiovascular disease, while 41% had previously had coronary revascularization (either coronary angioplasty, coronary bypass surgery, or both). In all, 3,829 patients (42%) had a baseline total cholesterol <5.5 mmol/L (213 mg/dl) (Table III). Due to the inclusion only of patients with a total cholesterol ≤7.0 mmol/L, the HDL cholesterol levels are lower than would be expected for an unselected population with CAD.[16–18]

Table IV compares the main features of patients randomized according to their qualifying event and sex. Patients with UAP were more symptomatic in terms of angina or dyspnea grade than those with a qualifying AMI ($p < 0.0001$), and had more often had coronary revascularization (58% vs 31%; $p < 0.0001$). More patients with AMI were receiving aspirin (84% vs 77%), β blocker (50% vs 41%), or angiotensin-converting enzyme inhibitor (18% vs 12%), but less were taking calcium antagonists (30% vs 43%) than were patients with UAP. Lipid profiles were similar whether the qualifying event was AMI or UAP.

Women entered into the study were slightly older than men and, with the exception of smoking habits, more often had other coronary risk factors: hypertension (56% vs 38%, $p < 0.0001$), obesity (18% vs 11%, $p < 0.0001$) and diabetes mellitus (10% vs 8%, $p < 0.01$). Women were more often symptomatic with angina or dyspnea ($p < 0.0001$), but fewer had previous coronary revascularization procedures (31% vs 43%, $p < 0.0001$), particularly less coronary bypass surgery (19% vs 32%). Lipid profiles were substantially different. Women had higher total, LDL, and HDL cholesterol levels than did men, but had lower total/HDL ratios. Fasting triglyceride levels were similar for both sexes.

DISCUSSION

The LIPID study is the largest ongoing study of the effects of cholesterol lowering in the secondary prevention of CAD. At the time LIPID commenced, most such studies in secondary prevention had not provided clear evidence of a reduction in coronary mortality, and the question as to whether total mortality would be reduced remained unanswered. More recently, meta-analyses of previous cholesterol-lowering trials have suggested significant reductions in total mortality for those at higher absolute risk of CAD mortality[19] and for patients with preexisting CAD.[20]

TABLE III Qualifying Serum Lipid Levels of 9,014 Patients Randomized to Pravastatin or Placebo*

	mg/dl	mmol/L	Number (%)
Total Serum Cholesterol			
	154–192	4.0–4.99	1,910 (21)
	193–212	5.0–5.49	1,919 (21)
	213–232	5.5–5.99	2,056 (23)
	233–251	6.0–6.49	1,817 (20)
	252–270	6.5–7.0	1,312 (15)
Lipid Fractions (median: 25th, 75th percentile)			
Total cholesterol	218 (196–240)	5.66 (5.09–6.22)	
HDL cholesterol	37 (30–42)	0.93 (0.79–1.08)	
LDL cholesterol	150 (131–167)	3.88 (3.39–4.37)	
Triglycerides	158 (105–193)	1.59 (1.18–2.18)	
Total/HDL ratio		6.07 (5.12–7.12)	
Apolipoprotein A-I (g/L)	130 (117–144)	1.30 (1.17–1.44)	
Apolipoprotein B (g/L)	133 (116–149)	1.33 (1.16–1.49)	

*Blood samples (fasted state) for lipids were obtained 4 weeks before randomization and were measured at a central lipid laboratory.
HDL = high-density lipoprotein; LDL = low-density lipoprotein.

TABLE IV Coronary Risk and Disease Severity by Qualifying Event and Sex in the LIPID Study

	Qualifying Event		Sex	
Baseline Characteristics and History	AMI (n = 5,754)	UAP (n = 3,260)	Men (n = 7,503)	Women (n = 1,511)
Age (yr) (median 25th, 75th percentile)	62 (54, 67)	63 (57, 68)	62 (55, 67)	64 (58, 69)
Women	862 (15)	649 (20)		
Qualifying Event				
UAP			2,611 (35)	649 (43)
AMI			4,892 (65)	862 (57)
Risk factors				
Current smoker	577 (10)	292 (9)	716 (10)	153 (10)
Ex-smoker	3,674 (64)	2,063 (63)	5,047 (67)	690 (46)
Systemic hypertension history	2,283 (40)	1,445 (44)	2,886 (38)	842 (56)
Diabetes mellitus history	484 (8)	293 (9)	621 (8)	156 (10)
Obesity (body mass index >30)	703 (12)	423 (13)	849 (11)	277 (18)
Other cardiovascular disease				
Claudication	508 (9)	396 (12)	724 (10)	180 (12)
Stroke	214 (4)	149 (5)	305 (4)	58 (4)
Transient ischemic attack	172 (3)	152 (5)	260 (3)	64 (4)
Angina grade (CCVS)				
No angina	3,863 (67)	1,823 (56)	4,869 (65)	817 (54)
No limitation (I)	1,516 (26)	1,064 (33)	2,067 (28)	513 (34)
Slight limitation (II)	340 (6)	333 (10)	505 (7)	168 (11)
Marked limitation (III)/at rest (IV)	35 (1)	40 (1)	62 (1)	13 (1)
Dyspnea grade (New York Heart Association)				
No dyspnea/no limitation (I)	5,273 (92)	2,883 (88)	6,853 (91)	1,303 (86)
Dyspnea on normal exertion (II)	475 (8)	376 (12)	643 (9)	208 (14)
Dyspnea on mild exertion (III)	6	1	7	0
Other treatment				
Aspirin	4,827 (84)	2,516 (77)	6,196 (83)	1,147 (76)
Beta blocker	2,887 (50)	1,322 (41)	3,481 (46)	728 (48)
Angiotensin-converting enzyme inhibitor	1,013 (18)	405 (12)	1,142 (15)	276 (18)
Calcium antagonist	1,705 (30)	1,388 (43)	2,428 (32)	665 (44)
Nitrates	1,634 (28)	989 (30)	2,092 (28)	531 (35)
Coronary revascularization				
Angioplasty only	497 (9)	491 (15)	802 (11)	186 (12)
Coronary bypass only	1,182 (20)	1,248 (38)	2,183 (29)	247 (16)
Both angioplasty and bypass	116 (2)	156 (5)	229 (3)	43 (3)
Lipids (mmol/L) (median 25th, 75th percentile)				
Total cholesterol	5.68 (5.10, 6.23)	5.63 (5.08, 6.19)	5.59 (5.04, 6.15)	5.98 (5.45, 6.48)
HDL cholesterol	0.92 (0.79, 1.07)	0.93 (0.79, 1.10)	0.90 (0.78, 1.05)	1.06 (0.90, 1.26)
LDL cholesterol	3.90 (3.40, 4.39)	3.87 (3.38, 4.34)	3.85 (3.36, 4.34)	4.07 (3.57, 4.53)
Triglycerides	1.59 (1.17, 2.20)	1.59 (1.18, 2.14)	1.59 (1.17, 2.19)	1.58 (1.19, 2.10)
Total/HDL ratio	6.12 (5.18, 7.15)	5.98 (5.03, 7.06)	6.17 (5.23, 7.20)	5.51 (4.60, 6.64)

Values are expressed as number (%) unless otherwise noted.
Abbreviations as in Tables I to III.

Importantly, a single large trial, the 4S (Scandinavian Simvastatin Survival Study)[21] has now demonstrated significant reductions in total mortality of 30% and in CAD mortality of 42% in a group of patients with CAD receiving simvastatin compared with those receiving placebo over a 5.4-year period. This trial provides the first clear evidence to confirm the results predicted from epidemiological data and earlier meta-analyses. However, several questions remain for which information from ongoing trials such as the LIPID study will be very important.

Indeed, the evidence from 4S and earlier secondary prevention trials reinforces the rationale for investigating whether lowering average or below-average cholesterol levels will also result in worthwhile benefits for those with CAD. The LIPID trial includes a substantial cohort with lower cholesterol levels, on average 1.0 mmol/L lower than those studied in 4S, with 42% having a total cholesterol level <5.5 mmol/L, the lower entry level for 4S. Several other differences in baseline characteristics between the 4S and LIPID populations, including the upper age cutoff and exclusion of patients with UAP from 4S, meant that over 80% of LIPID study participants would have been ineligible for 4S.

An important design feature of the LIPID trial is that clinical management other than trial medication is at the discretion of doctors managing individual patients. This allows for changing thresholds in treatment practice in terms of lipid-lowering therapy, which could arise following publication of other contemporary studies. Therefore, if at any time during the trial it becomes reasonably certain that cholesterol-lowering therapy is indicated for a particular individual, then such treatment can be prescribed. Such drop-ins to treatment have been allowed for in the power calculations.

Four smaller controlled trials of pravastatin versus placebo, designed to assess changes in atherosclerosis, have also been recently completed.[22–26] Individually, each trial demonstrated only modest effects on atherosclerosis, but collectively they demonstrated significant reductions in clinical events. However, the studies, individually or combined, were not of sufficient size to test for any effects on CAD mortality, as is being studied in the LIPID study. Similarly, it is recognized that the LIPID study does not have sufficient power to detect a modest decrease in total mortality, but should contribute important information on this outcome in 2 prospective meta-analyses.

The Prospective Pravastatin Pooling Project[27] will combine the results of LIPID with 2 other large randomized trials using the same dose and duration of pravastatin: the Coronary and Recurrent Events trial[28] and the West of Scotland Coronary Prevention Study.[29] The Cholesterol Treatment Trialist's Collaboration[30] involves these same 3 trials, 4S, and 8 other ongoing trials. Both overviews, designed before the results of individual trials were known, will help determine more reliably the effects of cholesterol lowering on cause-specific mortalities, as well as on coronary events within particular subgroups.

APPENDIX*

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*Former members are shown in square brackets.

†The Management Committee has overall scientific responsibility for the Study. National Heart Foundation and Bristol-Myers Squibb representatives are nonvoting members and may be excluded from meetings should the need arise to maintain the independence of the Committee.

‡The National Health and Medical Research Council (NHMRC) Clinical Trials Center is responsible for data management and trial coordination with participating centers. Data analyses are performed independently of the National Heart Foundation and Sponsor.

§The Safety and Data Monitoring Committee, appointed directly by the National Heart Foundation of Australia, consists of recognized experts, none of whom is a member of the Management Committee or its subcommittees, is a Principal Investigator at a clinical center, nor has any affiliation with the Sponsor.

C; Gold Coast Hospital: Aroney G, Hicks P, Kennedy P; Ipswich Hospital: LeGood H, Scott I; Maryborough Hospital: Anderson K, Ekin F, Real G; Nambour Hospital: Coverdale S, Elder R, Smith-Orr V; Pindara Hospital: Wicks B, Wicks J; Prince Charles Hospital: Carle A, Hasking G, West M; Princess Alexandra Hospital: O'Brien D, Ross-Lee L, Woodhouse S; Queen Elizabeth II Hospital: Boyd K, Roberts K, Sampson J; Redcliffe Hospital: Carroll P, Chaseling D, Ferry L; Repatriation General & Wesley Hospitals: Colquhoun D, Hicks B, Humphries J; Rockhampton Base Hospital: BaPe R, Currie B, Ewart A, Gnanaharan C, Smith H; Royal Brisbane Hospital: Atkinson C, Bradfield R, Cameron G, d'Emden M, Nye J; Toowoomba Hospital: Halliday C, Halliday R, Hughes L; Townsville Hospital: Graham K, Gunawardane K, Tan Y. **South Australia:** Flinders Medical Center: Aylward P, Hopkins M, Keynes S, Thomas C; Port Lincoln Hospital: Dufek A, McLeay R; Queen Elizabeth II Hospital: Herewane K, Horowitz J, Wilson L, Zhang C; Repatriation General Hospital: Calvert A, Crettenden J, Dunn B, Dunn G, Hamilton-Craig I; Royal Adelaide: Bradley J, Brown M, McLeay L, Ng L. **Western Australia:** Fremantle Hospital: Burton R, Garrett J, Lane G, Nullmeyers M, O'Neill M, Oshea J, Woollard K; Royal Perth Hospital: Brooks M, Gotch-Martin K, Hockings B; Sir Charles Gairdner Hospital: Bradshaw P, Hargan J, Ross S, Thompson P. **Tasmania:** Launceston Hospital: Pirani D, Singh B, Smith S, Wells A; North West Regional Hospital: D'Silva D, Parkes R, Templer M, Whitehouse N, Xu X; Royal Hobart Hospital: Kimber V, Kirkland G, Rundall S, Thomson A. **New Zealand:** Ashburton Hospital: Allen-Narker R, Baskaranathan S, Cook T, Gluyas M, Williams M; Auckland Hospital: Brown J, Hall A, Sharpe N; Christchurch Hospital: Alley T, Bridgman P, Ikram H, Jardine D, Skjellerup K; Dunedin Hospital: Armstrong L, Scott D, Stewart R, Wilkins T; Gisborne Hospital: Clarke D, Reddy J, Walters D; Green Lane Hospital: Denton M, Elliott J, Hamer A, Patel H, Pearce L, Reid P, White H; Hutt Hospital: Doone A, Mann S, Marchant R; Memorial Hospital: Hall K, Kenyon J, Luke R; Middlemore Hospital: Coxon R, Scott J, Williams M; Napier Hospital: Gibson L, Lewis G; Nelson Hospital: Barclay P, Clark M, Fry D, Kirk T; North Shore Hospital: Clague A, Hart H, Wright P; Northland Base Hospital: Calton J, Rankin R; Southland Hospital: Reuben S, Scobie P; Taranaki Hospital: Anandaraja R, Anandaraja S, Vitarachy A; Tauranga Hospital: Bruning J, Nairn L; Timaru Hospital: Frenneux C, Frenneux M, Roy D, Roy H; Waikato Hospital: Friedlander D, Low E; Wairau Hospital: Healy P, Hedley J; Wellington Hospital: Easthope R, Heuser P, Leslie P, McHaffie D, Thompson R.

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