Clinical and Angiographic Outcome Following Percutaneous Coronary Intervention

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Thesis submitted for the degree of Doctor of Medicine of the University of Auckland, 2001.

Dedication

To the women in my life – my dear wife Jan and my lovely daughters, Anna and Emily. I thank them for their love and support and attempts to understand my reasons for producing this book. Without their support and encouragement I could not have completed this work.

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Acknowledgements

I am deeply grateful to my wife Jan, and daughters Anna and Emily, for their love, support and encouragement, and for following me around the world to The Netherlands in order to complete my training as a cardiologist.

I would like to thank my mentors and friends at Green Lane Hospital for encouraging me to follow my interests and aspirations, in particular Dr Trevor Agnew, Dr John Neutze, the late Dr Tony Roche, Dr Toby Whitlock, Dr Edward Harris, Dr Eve Seelye and Sir Brian Barratt-Boyes.

I am indebted to my supervisors, teachers and mentors in the Netherlands who have become my friends; Dr Pim de Feyter, Professor Patrick Serruys, Dr Victor Umans, Dr David Foley, Dr Peter de Jaegere, Dr Marcel van den Brand, Dr Wim van der Giessen, Dr Aggie Balk and Professor Martin Simoons. They encouraged me to develop my skills as an interventional cardiologist, researcher and writer.

On returning to New Zealand and my "home" - Green Lane Hospital, I am deeply grateful to my colleagues and friends: Dr John Ormiston, Dr Mark Webster, Dr Jim Stewart, Dr Arthur Coverdale, Dr Warren Smith and Professor Harvey White, for their encouragement and support. They have fostered my research, and motivated me to complete this thesis.

Most of those named above have been collaborators and coinvestigators and have therefore also contributed significantly to the contents of my thesis.

I am grateful to my good friends Pip Poole and Paul Gilkison for their support and also for the sharing and enjoyment of "time-out" activities. Finally I would like to thank my parents for always being there. I thank them for the sacrifices they made and their quiet and unfaltering support.

Research Aims

1. To document and provide evidence to cardiologists, the medical community, patients and ourselves that percutaneous coronary intervention is a safe and efficacious treatment for patients with obstructive coronary lesions.

2. To provide evidence that stent implantation is an advance over balloon angioplasty, in the management of patients with coronary disease.

3. To provide evidence that "extending the boundaries" in terms of the types of patients and lesions that we treat, and modification of technique and equipment, is safe and efficacious with respect to adverse clinical outcomes.

4. To provide evidence that "extending the boundaries" does not significantly increase the chance of restenosis, which remains the "Achilles heal" of interventional cardiology.

5. To continue to search for information that allows us to stratify patients such that we can treat them in a more informed way.

6. To continue to search for information, on which to base a more informed forecast of what the intermediate and longer term outcomes might be, for patients with coronary artery disease.

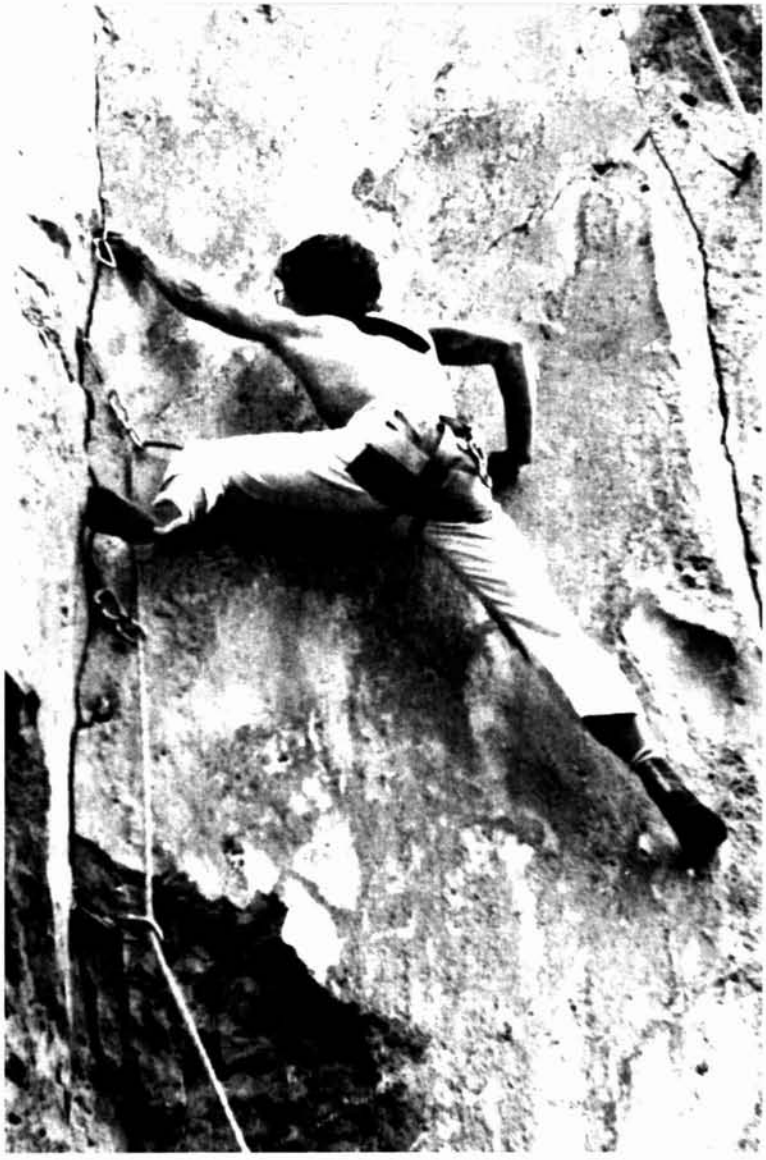
Introduction

Despite the finding that the age-adjusted rates for coronary artery disease have been falling in New Zealand and Australia for several decades, coronary heart disease remains the largest cause of premature death in people under the age of 70 years. With the ageing population and accumulating evidence that a more aggressive interventional strategy is beneficial for patients with coronary artery disease, we are continuing to see increasing numbers of patients referred for investigation and subsequent revascularisation procedures, both percutaneously and surgical. It will be many decades before we begin to see the benefits of more aggressive primary prevention strategies.

Coronary angioplasty, which was introduced in 1977 by Andreas Gruentzig, has become established as a safe and effective treatment strategy for patients with obstructive coronary lesions. Two major limitations of the technique remain. Introduction of a metal device, usually stainless steel, into the circulation causes platelet activation and thrombus formation and in 1-2% of cases, stent thrombosis and acute occlusion can occur. Restenosis, the process of neointimal proliferation, can cause a significant renarrowing of the treated segment. This occurs in approximately 20% of patients who then require a further intervention within the first 6 months of the initial treatment.

In order to advance and refine the practice of interventional cardiology and to improve outcomes, innumerable hours of research have been undertaken and volumes of papers published. Every piece of research in a small way contributes to the improvement in the care of patients with coronary artery disease.

We can use the analogy of a rock-climber (figure). When a rock-climber leads up a rock face, he carefully wedges stoppers into cracks and fissures and loops his rope through a carabiner before advancing. Should he fall he trusts that he will be held by the last inserted stopper. If he is cautious he will position many stoppers close together. If he is bold, less will be placed further apart. Coronary artery disease is like the rock face. Percutaneous coronary intervention is a route up the rock face that the climber has chosen to take, and related research, the stoppers. The practice of interventional cardiology appears, on occasion, to advance ahead of data from published studies, but research must continue so that if uncertainty should arise we will only fall as far as the most recent relevant published information. The more stoppers in the rock face, and analogously, the more studies that are undertaken and reported, the shorter the distance to fall.



The aim of this thesis is to contribute some of the stoppers for the rock wall and thus in a very small way help advance the practice of interventional cardiology in patients with obstructive coronary disease.

Abstract

This volume contains a series of linking chapters that follow the evolution of percutaneous intervention from conventional balloon angioplasty in the early to mid 1990s to stent implantation, which has now become standard practice. It describes contributions to the extension of clinical situations in which percutaneous intervention has been found to be efficacious as well as refinements in practice and technique. I was fortunate to have been a fellow and then staff member of the Cardiology department of the Thoraxcenter, Rotterdam from 1993-1995, which was then, and remains, at the forefront of the development of percutaneous coronary interventional techniques. My continued links with the Thoraxcenter as well as new projects have allowed me to continue my research and complete this thesis.

Part 1 contains two chapters on balloon angioplasty which was standard clinical practice for suitable obstructive coronary lesions until the mid 1990s.

The first chapter describes an audit of immediate clinical outcome and thus rates of procedure related complications of contemporary practice in a high volume unit following 970 balloon angioplasty procedures over a one-year period. Although the rate of adverse events appeared to remain static when compared to the previous decade, the requirement for emergency bypass surgery appeared to be diminishing and it is suggested that may be due to the increasing availability of stents for "bail-out".

The second chapter studies the long-term outcome with respect to major adverse clinical events in 856 consecutive patients treated by balloon angioplasty from 1980-1985. Although the long-term outcome was good and comparable to results of coronary bypass surgery, most patients suffered a further cardiac event during the 10 years following balloon angioplasty, most of which were repeat revascularisation.

Part 2 contains four chapters that describe and document contributions to the evolution of percutaneous coronary interventional practice from balloon angioplasty to stent implantation.

Chapter 1 is a review of the literature that describes the evolution of stenting from early animal experiments through early human studies to current practice and on to a vision of the future.
Chapter 2 describes follow-up of patients enrolled in the Benestent I study, which was pivotal to the introduction of stenting into clinical practice. Patients, in many centres world-wide, were randomised to balloon angioplasty or stent implantation and underwent 6-month clinical and angiographic follow-up. We report the extended one-year clinical outcome.

Chapter 3 documents the landmark Benestent II study. This was a randomised comparison of 827 patients in many centres worldwide (including Auckland) who were allocated to balloon angioplasty or a heparin-coated stent plus treatment with the anti-platelet agent ticlopidine. Patients randomised to stent implantation suffered fewer adverse events and less restenosis but this treatment was found to be more costly than balloon angioplasty.

Chapter 4 analyses in more detail some data from the Benestent II study. As well as being randomised to balloon angioplasty or stent implantation, patients were also sub-randomised to 6-month clinical only or clinical and angiographic follow-up. We therefore set out to assess whether management and outcome were influenced as a result of a follow-up angiogram. We found that more interventions were undertaken in those who underwent angiography with no adverse effect on outcome.

As a result of the above and other studies, stenting has become routine clinical practice with most patients (approximately 90%) undergoing percutaneous coronary intervention receiving a stent. Part 3 describes several studies which have expanded our knowledge of stenting in various clinical situations and conditions, and also incorporates studies that have added refinement to the technique of stenting.

Chapter 1 studies the intermediate term clinical outcome of stent implantation in degenerated saphenous vein grafts. Although the immediate outcome is good, with respect to adverse clinical events, the long-term benefit is limited indicating that with the available technology and medication, percutaneous treatment of vein graft is a palliative procedure.

Chapter 2 describes the results of a prospective multicentre study assessing the outcome of stenting long native coronary artery lesions. The rates of restenosis were acceptable. The study also provides us with an opportunity to analyse, using quantitative coronary angiography, the location of, and give insights into, the mechanism of the restenosis process.

Chapter 3 studies the outcome of stenting smaller coronary arteries. Its unique design, in that patients were required to have a lesion in a "small" and a "large" vessel, has provided us with the opportunity to compare both the rates and nature of the restenosis process in the same patients. In this way we abolished clinical and procedure related variables that confound the results when using historical comparisons.

Chapter 4 describes the introduction of a new stent, the MultiLink stent, into everyday clinical usage. As with all new devices and minor variations of contemporary devices, which slowly undergo small progressive changes, a careful assessment and audit must be undertaken to ensure it has resulted in improvement in, or at least no detriment to patient care. This chapter audits the clinical outcome of a new stent implanted in the first 126 patients in Auckland and Monash Medical Centre, Melbourne.

Chapter 5 is a study that tests a refinement in interventional technique. With refinement and miniaturisation of angioplasty equipment including the profile of balloons and stents, the possibly of implanting a stent without predilating the lesions with a balloon was raised. In this study 81 patients with suitable coronary artery lesions were randomised to stenting with and without predilatation. It was found that in selected patients a strategy of direct stenting was feasible, faster and more rapid than stenting after predilatation.

Chapter 6 describes a study which analyses data from 10 studies co-ordinated and managed by the Cardialysis core laboratory in Rotterdam. The inclusion of risk factors allows the opportunity to perform meta-analyses looking for factors that may influence outcomes. In this case we attempted to identify clinical and angiographic factors that influence asymptomatic restenosis following percutaneous coronary intervention.

Chapter 7 gives an overview of angioplasty numbers and practice in New Zealand by summarising data from the National Angioplasty Registry for the years 1995-1998. This period saw a steady growth in patients with coronary artery disease treated by percutaneous intervention and the number of patients who received stents rose from 23% in 1995 to 84% in 1998. This data attests to the data and results of the earlier studies reported in this thesis.

Statutory Declaration

I, Peter Nicolas Ruygrok, candidate for the degree of Doctor of Medicine of the University of Auckland, hereby state and declare as follows:

1. That in the research described in Part 1 Chapter 1 entitled "Immediate Outcome Following Coronary Angioplasty", the design and execution of the study, analysis of data, interpretation of results and preparation of the manuscript were largely my own work. This work was undertaken during my period of postgraduate training in The Netherlands. The work has been published in the *European Heart Journal* 1995; 16 Suppl L: 24-29. I was the first author and co-authors were Peter de Jaegere, Jan Verploegh, Ron van Domburg and Pim de Feyter.

2. That the research described in Part 1 Chapter 2 entitled "Clinical Outcome 10 Years After Percutaneous Transluminal Coronary Angioplasty", the design and execution of the study, interpretation of results and preparation of the manuscript were largely my own work. The analysis of data and production of survival curves was performed by Ron van Domburg. This work was undertaken during my period of postgraduate training in The Netherlands. The contents of this work has been published in the *Journal of the American College of Cardiology* 1996;271669-77. I was the first author and co-authors were Peter de Jaegere, Ron van Domburg, Marcel van den Brand, Patrick Serruys and Pim de Feyter.

3. That the research and writing of this review of the literature entitled "Intracoronary Stenting: From Concept to Custom" is predominantly my own work (Part 2 Chapter 1). I was guided by the wisdom and knowledge of Professor Patrick Serruys. This review was published in *Circulation* 1996; 94:882-889, as a "Bench to Bedside" feature article. Professor Serruys was a co-author of the paper.

4. That the research described in Part 2 Chapter 2 entitled "Continued Benefit of Coronary Stenting Compared to Balloon Angioplasty: One Year of Clinical Follow-up of the Benestent I Study" was performed and collated by staff of the Cardialysis Core laboratory, Rotterdam. My contribution was to the design of the one-year follow-up study, interpretation of the results and by writing the manuscript. The contents of this research have been published in *the Journal of the American College of Cardiology* 1996;27:255-61. I was third author of the paper; the co-authors were: Carlos Macaya, Patrick Serruys, Harry Suryapranata, Gust Mast, Silvio Klugman Philippe Urban, Peter den Heijer, Karel Koch, Rudiger Simon, Marie-Claude Morice, Peter Crean, Hans Bonnier, William Wijns, Nicolas Danchin, Claude Bourdonnec, Marie-Angele Morel.

5. That the research described in Part 2 Chapter 3 entitled "Randomised Comparison of Implantation of Heparin-Coated Stents with Balloon Angioplasty (Benestent II)" was a large randomised multicentre study co-ordinated by the Cardialysis core laboratory in Rotterdam. My contribution was to the concept of the study, to enrolling patients into the study and treating them in both Rotterdam and Auckland, in performing the follow-up clinical assessments for the Auckland patients and in addition I chaired the international critical events committee for this pivotal study. The study was published in *Lancet* 1998;352:673-81. I was a co-author of the paper with the first author and co-authors being: Patrick Serruys, Ben van Hout, Hans Bonnier H, Victor Legrand, Euglio Garcia, Carlos Macaya, Eduardo Sousa, Wim van der Giessen, Antonio Colombo, R. Seabra-Gomes, Fredinand Kiemeneij, John Ormiston, Hakan Emanuelsson, Jean Fajadet, Michael Haude, Silvio Klugman and Marie-Angele Morel.

6. That the research described in part 2 Chapter 4 entitled "Influence of 6 month Follow-up Coronary Angiography on Clinical Management and Outcome" was based on data collected for the Benestent II study (see above). The concept and study design were my own. Rein Melkert performed the data analysis. Interpretation of the data and writing of the chapter and manuscript were predominantly my own work with the assistance of the co-authors. The content of this chapter was published in the *Journal of the American College of Cardiology* 1999;34:1507-11. I was the first author and co-authors were: Rein Melkert, Marie-Angele Morel, John Ormiston, Frits Bar, Francisco Fernandez-Aviles, Harry Suryapranata, Keith Dawkins, Claude Hanet and Patrick Serruys.

7. That the research contained in Part 3 Chapter 1 entitled "Clinical Outcome Five Years After Stent Implantation in Saphenous Vein Grafts" was contributed to significantly by myself. The study concept and data collection were performed by Peter de Jaegere. I assisted with data analysis and in the writing of the manuscript which was published in the *Journal of the American College of Cardiology* 1996;28:89-96. I was the fourth author. The first author and co-authors were: Peter de Jaegere, Ron van Domburg, Pim de Feyter, Wim van der Giessen, Marcel van den Brand and Patrick Serruys.

8. That research contained in Part 3 Chapter 2 entitled "Stenting of Long Coronary Lesions: 6 month clinical and angiographic outcome" was significantly contributed to by myself. I contributed to the study concept and design, enrolled patients and clinically reviewed and performed all the follow-up angiograms on all the locally recruited patients. I contributed to the writing of the manuscript, which has been submitted for publication. I am the second author. The first author is John Ormiston and co-authors are: Mark Webster, Ian Meredith, Sue Price, Justin Ardill, Chris Buller, Don Ricci, Charles Chan, Gerry Devlin, Jim Stewart, Ian Penn and Mark Simmonds.

9. That the research described in Part 3 Chapter 3 entitled "Stenting of Lesions in Small and Large Diameter Coronary Arteries in the Same Patient: 6-Month Clinical and Angiographic Results" is predominantly my own work. I was the principal investigator of this multicentre study and with the steering committee designed the study. I recruited patents, with the assistance of co-investigators, reviewed them and performed all the follow-up angiograms on all the locally recruited patients. I wrote the manuscript with the assistance of co-investigators, in particular Mark Webster. This research has been submitted for publication. I am the first author. The co-authors are: Justin Ardill, Charles Chan, Ian Meredith, Jim Stewart, John Ormiston, Sue Price and Mark Webster.

10. That the research contained in Part 3 Chapter 4 entitled "Introduction of the Multilink Stent Into Routine Practice: Early Angiographic and Clinic Outcome" was a two centre study (Auckland and Melbourne) with the greatest contribution to the work coming from myself. I contributed significantly to the study design, data collection analysis and the writing of the manuscript. This research has been published in *catheterisation and Cardiovascular Diagnosis* 1998;43:147-52. I was the first author and the co-authors were: Gary Barron, John Ormiston, Ian Meredith, Mark Webster, Richard Harper, Andris Saltups, Barbara O'Shaughnessy and Jim Stewart.

11. That the research described in Part 3 Chapter 5 entitled "A Randomised Study of Direct Coronary Stent Delivery Compared with Stenting after Predilatation" was contributed to by myself. I assisted with study design, recruitment of patients and collation, interpretation and critique of the manuscript. The research has been published in the journal *Catheterisation and Cardiovascular Diagnosis* 2000;50:377-381. John Ormiston was the first author and I the third author. Other co-authors were: Mark Webster, John Elliott, Mark Simmonds, Ian Meredith, Gerry Devlin, Jim Stewart, Simon Dixon, Sue Price Chris Ellis and Teena West.

12. That the research described in Part 3 Chapter 6 entitled "Clinical and Angiographic Factors Associated with Asymptomatic Restenosis Following Percutaneous Coronary Intervention" was predominantly my own. Data from 10 large studies contained in the Cardialysis database, Rotterdam, was analysed by Vincent de Valk and interpreted and collated by myself. I was responsible for the concept and study design. I wrote the manuscript, with the assistance of Mark Webster, which has been accepted for publication in *Circulation*. The co-authors are: Mark Webster, Vincent de Valk, Gerrit-Anne van Es, John Ormiston, Marie-Angele Morel and Patrick Serruys.

13. That the research contained in Part 3 Chapter 7 entitled "Coronary Angioplasty in New Zealand 1995-1998: A Report From the National Angioplasty Registry". The database was maintained and analysed by Barbara O'Shaughnessy. The study concept, data interpretation and writing of the manuscript was predominantly my own. This data has been published in *The New Zealand Medical Journal* 2000;113:381-4. I was the first author with the co-authors being John Ormiston and Barbara O'Shaughnessy.

I further state THAT none of the work identified as being my own in (1) to (13) above has previously been accepted for the award of a degree or diploma in this or any other university and is not being concurrently submitted for a degree or diploma in any other university.

Signed by me [Removed]

Witnessed by [Removed]

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