CHAPTER 1: INTRODUCTION
Chapter 1: Introduction

The aim of the body of work in this thesis was firstly to identify, evaluate, and synthesise the evidence available from randomised trials of immunosuppressive drugs used to treat kidney transplant recipients, to determine which therapies were most likely to improve graft and patient survival over the short to medium term, and to quantify their draw-backs. My second aim was to investigate cancer risk in the transplant population in relation to the general population, and to establish cancer risk stratification for different patient groups through investigation of the association of cancer with un-modifiable recipient factors. These aims promote the underlying theme of the thesis: to inform and improve outcomes for recipients of kidney transplants.

This chapter provides context for the topic of end stage kidney disease (ESKD), outlines the relevant clinical uncertainties that surround kidney transplantation, and explains how the body of work in the following chapters of this thesis has sought to inform these uncertainties. There is no formal chapter of ‘literature review’, as chapters 2-5 are systematic reviews of the randomised trial literature, and chapters 6 and 7 incorporate relevant literature review in their background and discussion sections.

**End Stage Kidney Disease**

Kidney transplantation is the treatment of choice for most patients with end-stage kidney disease, as a transplant confers both survival and quality of life advantages over dialysis. The mortality rate on dialysis is 10-15% per year, compared with 2-4% per year post-transplantation. In the developed world there are approximately 350 people per million with a functioning kidney transplant. The incidence of treated ESKD is approximately 100 per million/year, which exceeds the transplant rate of around 30 per million/year.

Demand for transplantation exceeds organ availability. In addition to efforts to increase the donor pool through living donation and the use of non-heart beating donors, strategies to prolong kidney allograft survival have become a priority.

**Immunosuppression**

Short-term graft survival is related to control of the acute rejection process. Immunosuppressive algorithms consist of antibody induction agents given briefly peri-transplantation together with ongoing initial, more intense
immunosuppression, and followed by longer-term, less intense maintenance regimens. Calcineurin Inhibitors (CNI) are the cornerstone of immunosuppression. Cyclosporin introduction in the early-1980s improved one-year graft survival from 60% to over 80%. Tacrolimus emerged as an alternative CNI during the early 1990s. More recently further new drug classes and agents have emerged.

Globally, the approach to immunosuppression differs. The use of antibody induction varies, with 70% new kidney transplants in the United States receiving an antibody, but only 28% in Australia. Most current immunosuppressive regimens in the immediate post-operative period include one of the CNI (cyclosporin or tacrolimus), an antimetabolite (azathioprine or mycophenolate) and corticosteroids, with 93% recipients in the United States, and 70% in Australia, being discharged from hospital after transplantation on combinations of these “standard therapy” drugs.

Registry and randomised trial data show that between 15-35% recipients undergo treatment for an episode of acute rejection within one year of transplantation, and so require a course of more intensive immunosuppression added to background therapy. Strategies for treating AR include high dose steroids, a (further) course of an antibody (Ab) preparation, the alteration of background immunosuppression, or combinations of these options. Despite the variation in approach to immunosuppressive algorithms among and within countries, short term graft survival is similar, and most kidney recipients can now expect a greater than 90% chance of a functioning transplant at one year.

Despite the improvements in short term graft survival, the rate at which grafts are lost after 5 years remains little changed, with an average annual decline of around 5%. Longer term graft survival is related to the control of chronic allograft nephropathy (CAN), an incompletely defined process characterised clinically by progressive deterioration in graft function, proteinuria and hypertension and pathologically by changes on biopsy. CAN arises in the context of a complex interplay among episodes of acute rejection and suboptimal immunosuppression, non-immunological factors such as donor organ characteristics and delayed graft function and the chronic nephrotoxicity of CNI. Recent evidence suggests that higher doses of CNI increase progression of histological markers of graft damage.


**Graft versus patient survival**

Despite survival benefits over dialysis, kidney transplantation is not without risk. Compared with the general population, transplant recipients are at increased risk of cardiovascular disease, cancer, infection and death and the relative mortality rate for kidney recipients after the first post-transplant year remains 4-6 times that of the general population. For transplant recipients who die with a functioning graft, in Australia in 2004, 22% of deaths were attributable to cardiovascular disease, 39% to cancer and 21% to infection.

Proven cardiovascular risk factors in the normal population, such as impaired glucose metabolism and diabetes mellitus, dyslipidaemia and hypertension, are more common in the renal transplant population. Most immunosuppressive agents affect these cardiovascular risk factors, but do so to different extents. To what degree recipient mortality and graft loss can be attributed to these risk factors, the direct toxic effects of immunosuppression, or cumulative effects of infection and rejection is much debated.

The elevated cancer risk after transplantation is thought to result from the interplay of immunologic and non-immunologic factors: the chronic uraemic state is carcinogenic and overall or cumulative exposure to immunosuppression disrupts both anti-tumour immunosurveillance and anti-viral activity, and may potentiate the carcinogenic effects of other agents such as sunlight. Additionally, some immunosuppressive agents promote carcinogenesis by mechanisms independent of their immunosuppressive effects. Viral infections (including herpes and hepatitis viruses) are clearly linked to some malignancies and chronic antigen stimulation from the transplanted organ, repeated infections and transfusions of blood products have also been implicated. Whilst an increased overall risk of malignancy and the particular elevated risk of some viral-related cancers has been generally accepted, the underlying risk patterns of cancer within the transplanted population as compared to the general population has been less well elaborated.

**Informing and improving outcomes**

The optimum method for assessing efficacy of drug interventions is through randomised controlled trials. The introduction of new immunosuppressive agents over the past two decades was accompanied by an array of randomised trials with diverse intervention algorithms. Many trial interventions combined a new drug with
Chapter 1: Introduction

an established drug produced by the same pharmaceutical company, many were international and multi-centred and so were reported many times in many countries, where others were smaller and less well publicised.

As a result there are many unanswered questions: it is unclear how beneficial effects of specific agents or combinations of agents should be balanced against their harmful effects, whether there is overall evidence of equivalence or superiority, or what the longer-term impact on continuing graft function and patient survival might be.

Cancer is an infrequent but clinically important event occurring in the medium and longer-term after transplantation. Randomised trials, restricted by time-frame and sample size, are generally not powered to detect differences in cancer incidence. The advantages of analysing large prospective cohort data with extensive follow-up are clearly apparent when addressing incidence and risk factors. The Australian and New Zealand Dialysis and Transplant Registry (ANZDATA) is unique among ESKD registries, with complete geographical population-based coverage since the initiation of renal replacement therapy for ESKD in Australasia in 1963. It is also the only ESKD registry with a uniform mechanism of reporting cancer diagnoses directly to the central registry rather than relying on linkage with external cancer registries. The epidemiology of cancer in the transplant population is incompletely understood, with many unanswered questions including whether elevated risk has a fixed relationship across age ranges relative to the general population, whether risk is elevated for all cancer types, how relative risk translates to absolute risk, and how to identify those at higher risk of cancer.

The following chapters attempt to distil evidence to answer some of the uncertainties surrounding optimum drug therapy (chapters 2-5), and to describe cancer risk (chapters 6-7) in kidney transplant recipients.