# Studying the short-term complications of kidney transplantation: from bed to bench

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# Chapter 1

## General introduction, objectives and outline of this thesis

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## General introduction

In patients with end-stage renal disease, renal replacement therapy is a prerequisite for survival and can be achieved by hemodialysis, peritoneal dialysis or kidney transplantation. Although the preferred option of renal replacement modality should be based on patient-centered medical practice, kidney transplantation is the most preferred option due to its advantages in terms of patient survival, quality of life and healthcare costs.[1-3]

One of the first successful kidney transplantation in humans was performed in 1954 between twin brothers in Boston, USA,[4] and ever since, organs retrieved from living donors and donation after brain death (DBD) donors have provided the vast majority of kidney grafts for transplantation globally.[5] However, its medical success as well as the increasing patient population (due to an ageing population and an increasing prevalence of kidney failure) has led to a substantial mismatch between kidney transplant demand and supply.[6,7] This is reflected by long waiting lists and has resulted in the death of many patients while waiting for kidney transplantation.

In an effort to reduce the waiting lists for kidney transplantation, transplantation of kidneys retrieved from controlled donation after circulatory death (DCD) donors has been proposed as an effective strategy to expand the donor pool.[5,8] In DCD donors, retrieval of organs for transplantation purposes is followed after death confirmed using circulatory criteria, and differs from DBD donors in whom death has been declared using neurological criteria.[9] As a consequence, DCD donors are, as opposed to DBD donors, exposed to an inevitable period of warm ischemia prior to laparotomy and cold flush (Figure 1).

Despite long-standing arguments that DCD kidney grafts may reduce the donor organ shortage, many countries remain highly reluctant toward the use of DCD grafts.[7,10] While for some countries this is based on legal restrictions, ethical issues or logistical concerns,[7] for the majority of countries this reticent attitude toward the use of DCD grafts generally reflects medical concerns that are based on a high incidence of early graft loss (EGL) and delayed graft function (DGF).[10-12] Whilst the loss of a kidney graft shortly after transplantation (i.e. EGL) is an obvious disastrous complication, there is also concern about DGF (the delayed functional recovery of a kidney graft as a clinical manifestation of ischemia-reperfusion (I/R) injury) as it has been associated with impaired renal function and impaired long-term graft survival.[13,14]

In the first part of this thesis, I will focus on whether the perception in clinical practice that transplantation of DCD kidneys is inferior to DBD kidneys and associated with more posttransplant complications is still correct. Obviously, if incorrect, the medical

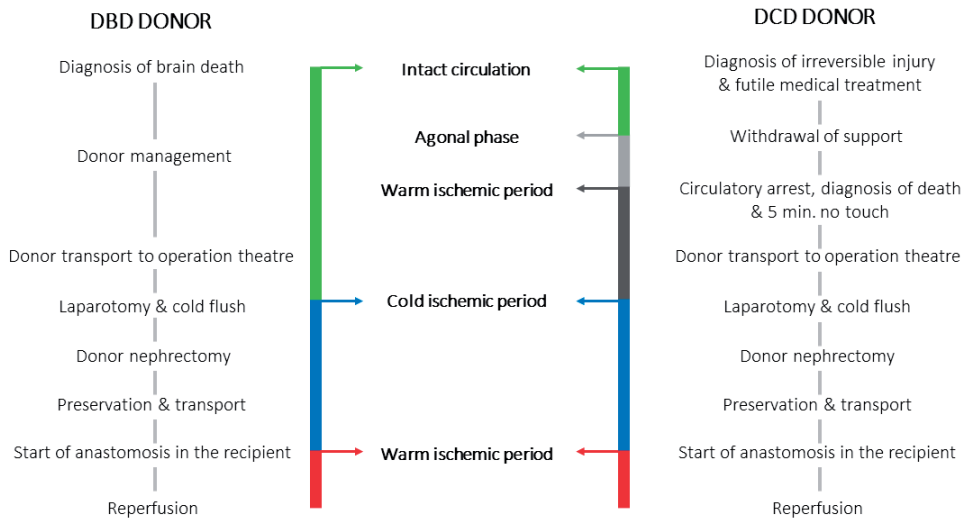


**Figure 1.** Clinical pathways of kidney organ donation after brain death (DBD) and circulatory death (DCD).

argument to abstain and not attempt to increase utilization of DCD kidneys is not justified. In the second part of this thesis, I will move from bed to bench in order to further elaborate on DGF (defined as the situation in which the recipient is temporarily dialysis dependent after transplant surgery) as the primary complication in DCD kidney transplantation and explore the challenges, opportunities and future perspectives in research focusing on I/R injury.

## Objectives and outline of this thesis

### Part I

While high incidences of EGL and DGF are considered major impediments to a more liberal use of DCD grafts, data from The Netherlands and the United Kingdom (in which DCD grafts currently account for ±50% of all deceased-donor kidney transplant procedures) show similar long-term survival outcomes after DBD and DCD kidney transplantation (Figure 2).[10,15,16] These observations are remarkable and contradict with the general perception that transplantation outcomes of DCD grafts are inferior to DBD grafts. Moreover, an explanation for contrasting short-term outcomes but equivalent long-term outcomes is lacking. In **the first part of this thesis**, we therefore aim to explore potential explanations for equivalent long-term survival outcomes of DBD and DCD kidney transplantation using an epidemiological approach.

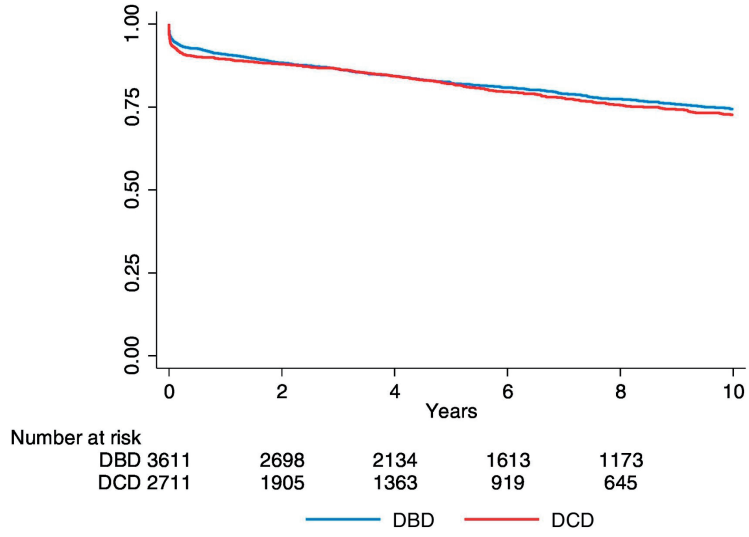


**Figure 2. Recipient death censored 10-year graft survival of donation after brain death (DBD) and circulatory death (DCD) kidney grafts transplanted between January 1st 2000 and January 1st 2017 in The Netherlands**. This figure was adapted from Schaapherder et al. [16]

First of all, following general introduction in **chapter 1** on deceased donor kidney transplantation, we focus in **chapter 2** on EGL as one of the most feared complications after DBD, but in particular in DCD kidney transplantation. Whilst in an era of severe organ shortages, many donor kidneys with an anticipated risk of EGL are declined for transplantation, the actual clinical consequences of EGL are currently unknown. Thus, in an attempt to estimate the optimal trade-off where the impact of EGL is balanced by the donor pool size, we first will perform a systematic analysis of the clinical consequences of early graft loss after deceased donor kidney transplantation in **chapter 2**. In **chapter 3** and **chapter 4** we subsequently aim to find an explanation for the contrasting short-term, but equivalent long-term survival outcomes of DBD and DCD kidney transplantation. In **chapter 3** we hypothesize that concerns regarding inferior DCD outcomes, often based on data from historical cohorts, are interfered by time-related effects and may therefore not apply anymore in our current era. To explore a possible effect of time on outcomes, we perform a time-dependent comparative analysis, and examine the current results achieved when transplanting kidneys from DBD and DCD donors. Next, in **chapter 4** we will search an explanation for the remarkable finding of chapter 3 that recipients of DBD and DCD grafts show graft survival equivalence, despite a persistent higher incidence of DGF in DCD grafts in the current timeframe. In this chapter we investigate whether this apparent paradox can be explained by differential impacts of DGF on DBD and DCD graft survival, and in addition we will attempt to explore its biological basis.

## Part II

In the second part of this thesis, we further concentrate on DGF as in many countries–even in an era of severe organ shortages–DGF remains a main reason to not or only cautiously allow DCD programs. Although the impact of DGF on graft survival may be less than commonly thought in DCD grafts (part I), DGF is still feared as it may negatively impact the short-term outcomes (i.e. prolonged hospitalization, increased healthcare costs, and impaired graft function).[13,14] Also, it should be stressed that DGF remains–albeit less prevalent–an important complication after DBD kidney transplantation with a delayed functional recovery that is associated with a lower graft survival rate.[16,17] Thus, in an effort to reduce the incidence of DGF, we move in the **second part of this thesis** to a more molecular approach, composing a theoretical model of the pathophysiology underlying DGF as a manifestation of I/R injury, and subsequently explore emerging challenges that will arise in *in vivo* and *in vitro* studies of I/R injury.

Although the pathophysiology of I/R injury is complex and not yet fully understood, recent reports indicate that I/R injury relates to critical metabolic deficiencies due to mitochondrial damage.[18-20] It is interesting, that although several studies have identified promising interventions ameliorating the detrimental effects of I/R injury, the majority of therapies is restricted to the preclinical setting, and a definitive solution treating or even preventing I/R injury is still missing in clinical practice.[21,22] In **chapter 5** we present a novel theoretical model and provide new insights into the pathophysiology of I/R injury in a clinical setting focusing on reductive stress. However, to further dissect this theory, more research is needed. While several avenues of research (e.g. clinical, preclinical and cell culture studies) are considered suitable to study the processes of I/R injury, each type comes with its own challenges and will be discussed in **chapters 6 and 7**. Although clinical studies are generally considered most desirable for future I/R studies, the availability of human tissue for research purposes remains limited and governance surrounding operational, legal or ethical access to obtain tissue are challenging. An alternative approach to unravel underlying processes of I/R injury is the use of preclinical (i.e. animal) studies. In the context of the existing translational gap,[21,22] **chapter 6** will elaborate on the question to what extent preclinical models of renal I/R injury can mimic the clinical setting, with a particular focus on methodological challenges and interspecies differences in metabolism. Given the putative interspecies metabolic differences as well as the limited availability of human samples for research purposes, we will also focus on cell culture experiments as another promising technique to study the pathophysiology of I/R injury.

**Chapter 7** highlights that metabolic (I/R) studies under cell culture conditions are profoundly interfered by the Crabtree effect, a phenomenon that describes the non-physiologic metabolic switch of cultured cells to a glycolytic phenotype.[23] Hence,

metabolic studies in cultured cells critically rely on reversal of this Crabtree effect. In **chapter 7** we therefore provide a systematic review of reported strategies aiming to circumvent the Crabtree effect in cell cultures. We also provide a critical appraisal of these strategies and present some recommendations for future research focusing on I/R injury and cellular metabolism.

## Part III

In the third and final part of this thesis the summary, future perspectives and conclusions of this thesis are presented (**chapter 8**).

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