ENGLISH SUMMARY

Background
Almost every human is born with two kidneys. They are located in the flanks, behind the peritoneum and have several important functions. The kidneys remove waste products from the blood, regulate blood pressure and fluid homeostasis. Furthermore, they produce several hormones and enzymes, which are (amongst others) involved in the regulation of bone mineralization and production of red blood cells. For all kind of reasons, the function of the kidneys can decrease over time or in some cases their function is already decreased or even absent at time of birth. When the function of the kidneys is decreasing, this can be noticed by a decreased filter function of the kidneys resulting in accumulation of waste products. Patients with a decreased kidney function (renal failure) might feel tired and apathetical.

When kidney function is deteriorating, at some given time, patients require a form of renal replacement therapy (RRT) (i.e. dialysis or renal transplantation). A patient has then reached End-Stage Renal Disease (ESRD).

ESRD leads to a variety of problems due to the failure of multiple functions of the kidney. Children with ESRD frequently suffer from anaemia, growth retardation, high blood pressure (hypertension) and bone mineral disorders (CKD-MBD). Furthermore, at an older age, they suffer from an increased risk for cardiovascular disease (CVD).

CKD-MBD is a serious disorder, especially in childhood, since the bone is a very dynamic tissue in these years as it is constantly growing. As a result of phosphate accumulation and decreased vitamin D metabolism, blood levels of calcium decreases. Next, the parathyroid secretes a hormone called parathyroid hormone (PTH) which stimulates the bone to release calcium. This causes a decreased bone mineral density (high turnover bone disease). However, when inappropriately treated by supplementation of vitamin D, an opposite phenomena can occur in which bone turnover decreases and the bone becomes hard, but less strong. At the age of 21 years peak bone mass is reached. When this process is disturbed, bone mineral accrual is altered, leading to weak bones and decreased final height. Earlier research has shown that up to 40% of young adults with ESRD since childhood suffer from bone disease, varying from bone pain to fractures or even handicaps. Due to the fact that, especially in children, bones are a dynamic organ, diagnosing and monitoring CKD-MBD is difficult.

Gold standard for diagnosing CKD-MBD is a bone biopsy. However, in paediatric care this is not indicated due to its invasive character and the need for staining with medications with adverse reactions. To date, it is unknown to which extent current imaging methods for diagnosing CKD-MBD in children are reliable and able to predict which patients are at risk for developing for example fractures. Besides symptoms such as bone pain, CKD-MBD affects final height. A decreased final height is associated with a decreased (health related) quality of life. Preventing or treating growth retardation is essential, for example by supplementing growth hormone (GH). However, several European studies have shown that GH is prescribed less often than indicated. It remains unknown why GH is prescribed less often. Possibly both doctor and patient related factors influence the prescription of GH.
Children with ESRD encounter a 55 times increased risk of dying as compared to their healthy peers. However, over time survival has increased, causing patients to be confronted with long term effects more frequently, such as CVD. Symptoms and signs of CVD in childhood may vary, hampering early and adequate diagnosing and monitoring. Current imaging methods, such as conventional echocardiography have shown to be unreliable.

Several studies have shown that transplantation is the preferred method of RRT. However, when this is impossible, peritoneal dialysis is preferred over haemodialysis. Apart from the beneficial health outcome, peritoneal dialysis has one big advantage: it can be performed at night when the child is sleeping. In contrast, when a child is on haemodialysis, it needs to be in the hospital up to 6 times a week during several hours, causing them to have less social interaction and social participation. In the Netherlands, 30 new children suffer from ESRD each year and need some kind of RRT. These children are treated in four, relatively small, centres (Utrecht, Amsterdam, Rotterdam and Nijmegen). Up to 2007 there was no structural consultation or collaboration between these centres. Since ESRD at childhood is rare, large scale studies assessing best practice are scarce. Due to a lack of evidence, differences may exist between and within centres. Therefore, in 2007, the Renal Insufficiency in Children – Quality assessment and improvement project (RICH-Q) was initiated. All four Dutch and six Belgian centres participated in this collaborative. The project aims to improve the quality of care for children with ESRD by central data registration, structural consultation, assessing best practices, produce uniform guidelines and study methods of monitoring of CVD and CKD-MBD.

This thesis
In this thesis quality of care and monitoring of CKD-MBD and CVD is assessed. Practices and policies with regards to transplantation, growth hormone and hypertension are inventories and compared with current guidelines and literature. Next, current methods of imaging of CKD-MBD and CVD are evaluated.

In the first part of this thesis (part I) a short overview of the current available knowledge is presented and the rationale for this thesis is discussed. Chapter 2 describes the differences in practices and policies with regards to kidney transplantation in children. Differences in policies between the RICH-Q centres are inventoried and compared with current available guidelines. This study showed considerable variations in policies between centres. For example, centres use a minimum accepted weight before transplantation as transplanting an adult kidney into a small child is technically challenging. However, the minimum accepted weight differed between 8 and 12 kilogram between centres. This implies that a child of 9 kilogram might be accepted for transplantation in one centre, but might spent up an extra one year on dialysis in another centre. Longer time on dialysis increases the risk of complications and even death. Furthermore, differences exist between the criteria of living and deceased donors, especially with regards to maximum accepted age. Some centres accepted a living donor with
a maximum age of 65, whereas other centres accepted donors with a lower maximum age. Again, treatment and hence outcome might differ between centres. These differences might be caused by a lack of evidence based guidelines. Since ESRD in childhood is rare, large scale studies are scarce and evidence for guidelines is lacking. Centres are dependent of expert opinion based guidelines or their own experiences. More research on the outcome of children with a renal transplant seems warranted in order to produce uniform guidelines enabling the same treatment and outcome for each child, independently of where the child is being treated. **Chapter 3** also assesses differences in policies, practices and guidelines, however at a larger scale. In this study, differences in policies between 28 European countries with regards to growth hormone are inventoried and compared with outcome, i.e. final height. Criteria for prescribing growth hormone varied between countries, possibly affecting final height. Whether a paediatric nephrologist was allowed to prescribe growth hormone affected final height the most. This study also showed that GH is prescribed less often than one would expect based on the stated criteria and the height of the patients. Incompliance and unjustified ideas on adverse reactions of growth hormone might contribute to the low prescription rate. Finally, financial hurdles might influence prescription behaviour. In **Chapter 4** prevalence and management of hypertension in paediatric and young adult kidney recipients is assessed. Both paediatric and adult nephrologists completed a questionnaire on the management of hypertension after renal transplantation. Data from the RICH-Q database and Dutch Organ Transplantation Registry (NOTR) were used to analyse the prevalence of (uncontrolled) hypertension. Hypertension was defined as a blood pressure above target without treatment or a blood pressure on or below target with medication. When there was a blood pressure above target with medication it was defined as uncontrolled hypertension. This study showed a higher prevalence of (uncontrolled) hypertension in young adults as compared to children with a renal transplant. This difference is possibly explained by a difference of follow-up between paediatric and adult nephrology care in which the follow-up of the adult patient is less strict and less controlled. Previous studies have shown different results with regards to the effect of transition (transfer from paediatric to adult care) on outcome. In this study no association was found between blood pressure and transition. There was an increase in blood pressure over time at an earlier age as compared to the healthy population in which blood pressure rises after the age of 40 years. Since high blood pressure is associated with adverse outcome, this warrants further research and deserves the attention of the professional involved in the care for the young adult kidney recipient.

In **Part II** the quality of monitoring of CKD-MBD and CVD is being evaluated. **Chapter 5** describes the reliability of Dual Energy X-ray Absorptiometry (DXA) to monitor CKD-MBD in ESRD. In this study, participants were studied in 2000 and 2010. The LERIC cohort consists of patients starting RRT before 1979 and aged <15 years at initiation of RRT. In 2000 survivors were extensively studied, in which bone mineral density (BMD) was assessed with the help of DXA. Participants showed a significantly decreased BMD as compared to healthy adults. In 2010, the same patients were asked to participate in a
follow up study in which signs and symptoms of CKD-MBD (such as bone pain, handicaps, fractures etc.) were inventoried. A majority of the patients reported to suffer from bone disease related symptoms. However, this study showed that BMD did not differ between participants with and without fractures or bone related symptoms. In the assessment of BMD by DXA, the bone is considered to be a two-dimensional object. However, in reality, it is a three-dimensional object in which BMD can be underestimated when ignoring the three-dimensional aspect. Therefore, we corrected BMD for height. Despite this correction, no association was found between BMD and fractures and/or bone related symptoms. Nephrologists caring for adult patients with childhood onset CKD-MBD should take this in consideration when interpreting DXA results.

In the second and last chapter of part II (Chapter 6) a new method to detect CVD was explored. Earlier research has shown that conventional echocardiography was not reliable in the detection of CVD. A new method, Speckle Tracking Echocardiography (STE), is an in part automated method which assesses the movement of different parts of the ventricular wall. In this study myocardial function of children with ESRD and healthy controls was assessed. Children with ESRD showed an impaired function of the left ventricle, without abnormal function as assessed with conventional echocardiography. Whereas with conventional echocardiography mainly left ventricular wall thickness is measured, with STE the function of different parts of the myocardium is measured. This provides the physician with information on the function of the ventricle rather than just left ventricular thickness or left ventricular mass index. In studies with adults, STE has shown to be a good predictor of CVD. To which extent this is also applicable for children with ESRD needs further research.

Part III describes how RICH-Q was initiated and to which extent this ‘quality improvement collaborative’ has been able to actually improve the quality of care (QOC). In this study quality indicators as registered in the RICH-Q database were analysed over time and compared with data from ‘rich’ European countries registered the ESPN/ERA-EDTA database. Several quality indicators showed a trend towards improvement, only height showed to be significantly higher in RICH-Q as compared to the ESPN/ERA-EDTA. Over time within RICH-Q, more children were pre-emptive transplanted and more frequently with a living donor kidney. This corresponds with the personal experiences of especially the Belgian doctors who stated to promote living related kidney donation more actively. This increase might improve outcome of Belgian children needing RRT. The lack of improvement in the other quality indicators may be explained by the fact that the QOC has reached a so called ceiling in which no further improvement is possible. QOC may be influenced by more than doctor related factors. Amongst others, compliance might contribute to the fact that, despite the efforts of physicians and nurses, no improvement could be measured. Furthermore, possibly QOC should be assessed by other, non-clinical, variables.

The RICH-Q project had led to three medical and one paramedical guideline possibly leading to more uniform care in the future. Furthermore, the project has provided more insight on the differences between centres and reliability of different methods to monitor
CKD-MBD and CVD. Finally, and possibly most important, involved nephrologists have stated to be willing to proceed with RICH-Q as they consider RICH-Q of great additional value in their daily practice.

In the last part of this thesis (General Discussion) the results as presented in this thesis are discussed. The studies have shown some important results with regards to the quality of care and monitoring in paediatric ESRD. There are several differences in policies and practices with regards to transplantation, growth hormone and hypertension. Differences that might affect outcome and might imply that more differences exist. The differences in policies could be explained by a lack of evidence based guidelines. Prospective studies, such as RICH-Q, seem essential in order to collect data and perform prospective studies. Furthermore, in absence of evidence based guidelines, with the help of a collaborative such as RICH-Q, multicentre uniform guidelines can be produced. This thesis has also shown that the current methods of imaging of CKD-MBD and CVD are unreliable. DXA seems unreliable for predicting which patients with ESRD are at risk for developing bone disease and/or fractures. More research to assess reliability and predictive value of newer imaging methods is needed.

Conventional echocardiography might not be reliable for the assessment of left ventricular function in children with ESRD. With the help of STE, changes in myocardial function can be seen even before noticed with conventional echocardiography. Although in adult studies abnormal STE appeared to be associated with increased risk of death, the role of STE in the follow-up of children with ESRD needs further research. In the last chapter, the effect of RICH-Q as a quality improvement project is evaluated. Although RICH-Q showed not to be able to improve QOC on all quality indicators, it did provide physicians with new and relevant results with possible consequences for daily practice. At the start of RICH-Q ambitious goals were set, which, in retrospect, might have been too ambitious. Over time, despite the effort of both doctors and nurses, a ceiling might have been reached with regards to QOC. This is possibly due to the fact that certain factors are present which cannot be influenced by the doctors or nurses. Furthermore, it could be possible that there is a difference in opinion between doctors and patients with regards to which outcome measurements and clinical variables are important. In the nearby future, patients’ opinion and needs will most probably become more important in scientific research.