Clinical and quality aspects of native and transplant kidney biopsies in Sweden

Björn Peters
To my family
# Table of Contents

Table of Contents

Abstract 

Abbreviations 

Original Papers 

Summary in Swedish/Sammanfattning på svenska 

Introduction 

- Anatomy of the kidney 
- History of kidney biopsies 
- Types of biopsy needles 
- Biopsy sample size and needle gauge 
- Biopsy methods 
- Indications and contraindications for kidney biopsies 
- Definition of biopsy complications (“major” and “minor” complications) 
- Type of biopsy complications and risk factors for kidney biopsies 
- Outpatient and inpatient biopsies 
- Antiplatelet drugs and kidney biopsies 
- Bleeding time and desmopressin in kidney biopsies 
- Resistive Index 
- Renal pathology 

Aims 

Study I 

Study II 

Study III 

Study IV 

Materials and Methods 

Study I 

Study II 

Study III 

Study IV 

Results 

Discussion 

Limitations of this thesis 

Conclusions 

Clinical recommendations 

Acknowledgements 

References 

ORIGINAL PAPERS
Abstract

Percutaneous kidney biopsies have been performed since 1944 to establish diagnoses and treatment. Risk factors based on a limited amount of data have shown age, blood pressure, kidney function and needle size as some risk factors for biopsy complications. Although the techniques of biopsy have improved over the years, it is still an invasive procedure and serious complications can occur.

The overall aim of this thesis was to obtain a large series of data from biopsy procedures and to use these to bring further light on risk factors to help minimize the risk for patients and to optimize diagnostics. Specific aims were to clarify if different factors, such as gender, diagnoses, localization of biopsies, needle types and sizes, could be useful to help minimize complication risks in native kidney biopsies (Nkb) and transplant kidney biopsies (Txb). Another point to investigate was the value of the Resistive Index (RI) obtained at ultrasound before performing Txb.

Materials and methods: A protocol for prospective multicentre registration of various factors and complications associated with Nkb and Txb was designed. Consecutive data were obtained from seven hospitals. All biopsies, except one computer tomography-guided Nkb, were performed using real-time ultrasound guidance and an automated spring-loaded biopsy device. For the biopsies 14- to 20-Gauge (G) needles were used. The kidney function level, i.e. estimated glomerular filtration rate (eGFR), was calculated using the Modification of Diet in Renal Disease (MDRD) formula (GFR in mL/min per 1.73m²). For statistical analyses the IBM SPSS Statistic 22 (Armonk, NY, USA) and OpenEpi (Open Source Epidemiologic Statistics for Public Health, www.OpenEpi.com) were used. Data were presented as Odds Ratio (OR), Risk Ratio (RR) and Confidence Intervals (CI). A two sided p-value of <0.05 was considered significant. In total 1299 consecutive biopsies (1039 native and 260 transplant kidneys) in 1178 patients (456 women and 722 men) were used for investigation. The median age of patients was 55 years (range 16 to 90 years). Major (require an intervention) and minor biopsy complications (no need of intervention) were registered.

Results: The overall frequency of biopsy complications for Nkb was 8.8% (major 6.7%, minor 2.1%) and for Txb was 6.5% (major 3.8%, minor 2.7%); no death. Women had a higher risk for development of major (10.7% versus 4.7%, OR 2.4, CI 1.4–4.2) and overall biopsy complications (13.2% versus 6.5%, OR 2.2, CI 1.4–3.5) compared to men in Nkb. In Nkb, major complications were more common after biopsies from the right kidney in women versus men (10.8% vs 3.1%, OR 3.7, CI 1.5–9.5), in patients with lower versus higher BMI (25.5 vs 27.3, p=0.016) and for younger versus older age (44.8 vs 52.3 years, p=0.002). Lower (90 mmHg) compared to higher (98 mmHg) mean arterial pressure in Txb indicated a risk of
major complications (p=0.039). Factors such as number of passes and kidney function did not influence complication rates. Biopsy needles of 16 G compared to 18 G showed more glomeruli per pass in Nkb (11 vs 8, p<0.001) and in Txb (12 vs 8, p<0.001). Sub-analysis revealed that 18 G 19 mm side-notch needles in Nkb resulted in more major (11.3% vs 3%, OR 4.1, CI 1.4-12.3) and overall complications (12.4% vs 4.8%, OR 2.8, CI 1.1-7.1) in women than in men. If the physician had performed less compared to more than four Nkb per year, minor (3.5% vs 1.4%, OR 2.6, CI 1.1-6.2) and overall complications (11.5% vs 7.4%, OR 1.6, CI 1.1-2.5) were more common. The localization of biopsy within the kidney (Nkb and Txb) was not a risk factor for complications. Patients with IgA-nephritis compared to patients with other diseases had a higher risk of major complications (11.7% vs 6.4 %, OR 1.8, CI 1.1–3.2). More major complications were found in Nkb if they had higher versus lower degree of glomerulosclerosis (31% vs 20 %, p=0.008) and in Txb if there was a higher versus lower degree of interstitial fibrosis (82% vs 33%, p<0.001). Re-biopsies (Nkb) were more common in patients with IgA-nephritis than those with other diseases (4.7% vs 1.3 %, OR 4, CI 1.5–11), in younger versus older age (42.6 vs 52.3 years, p=0.031), and in those with a higher versus lower degree of interstitial fibrosis (63% vs 34 %, p=0.046). In Txb, a RI≥0.8 compared to RI<0.8 predicted major (13.3% vs 3.2%, RR 4.2, CI 1.3-14.1) and overall biopsy complications (16.7% vs 5.3%, RR 3.2, CI 1.2-8.6). In the group <0.8, RI correlated with age (r_s=0.28, p<0.001) and systolic blood pressure (r_s=0.18, p=0.02). In the group ≥0.8, RI correlated with degree of interstitial fibrosis (r_s=0.65, p=0.006) and systolic blood pressure (r_s=0.40, p=0.03). The multiple regression analysis showed that the <0.8 RI group correlated only with age (p<0.001), whereas the ≥0.8 RI group correlated only with the degree of interstitial fibrosis (p=0.003).

Conclusions: The present results motivate greater attention to be paid to the possibility of major side-effects after Nkb in women and biopsies from their right side, but as well in younger patients, and in those with lower BMI. This also applies for patients with presumptive IgA-nephritis and higher degree of glomerulosclerosis. In Txb, patients with higher degree of interstitial fibrosis had a greater risk of major complications. Moreover, the present data indicate that Nkb and Txb should be preferably taken with 16 G needles with 20 mm sample size. This results in better histological quality and there is a lower risk for major complications as compared to 18 G needles. The localization of biopsy within the kidney (Nkb and Txb) does not alter complication rates. For Nkb there were fewer complications if the physician had performed at least four biopsies per year. A RI≥0.8 in Txb indicates a greater risk for major and overall complications.
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ALP</td>
<td>Alkaline Phosphatase</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine Aminotransferase</td>
</tr>
<tr>
<td>aPTT</td>
<td>Activated partial thromboplastin time</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate Aminotransferase</td>
</tr>
<tr>
<td>A/L</td>
<td>Arteries per total length of biopsy specimen (i.e. arteries per mm)</td>
</tr>
<tr>
<td>A/P</td>
<td>Arteries per pass</td>
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<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>CI</td>
<td>Confidence Intervals</td>
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<tr>
<td>CRP</td>
<td>C-reactive protein</td>
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<tr>
<td>eGFR</td>
<td>Estimated glomerular filtration rate</td>
</tr>
<tr>
<td>eGFR MDRD</td>
<td>eGFR according Modification of Diet in Renal Disease</td>
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<tr>
<td>ESR</td>
<td>Erythrocyte sedimentation rate</td>
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<tr>
<td>G</td>
<td>Gauge</td>
</tr>
<tr>
<td>GN</td>
<td>Glomerulonephritis</td>
</tr>
<tr>
<td>GS</td>
<td>Glomerulosclerosis</td>
</tr>
<tr>
<td>G/L</td>
<td>Glomeruli per length of biopsy specimen (i.e. glomeruli per mm)</td>
</tr>
<tr>
<td>G/P</td>
<td>Glomeruli per pass</td>
</tr>
<tr>
<td>IF</td>
<td>Interstitial fibrosis</td>
</tr>
<tr>
<td>INR</td>
<td>International normalized ratio</td>
</tr>
<tr>
<td>L/P</td>
<td>Length of biopsy specimen per pass (mm)</td>
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<tr>
<td>MAP</td>
<td>Mean arterial blood pressure</td>
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<tr>
<td>Nkb</td>
<td>Native kidney biopsy</td>
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<tr>
<td>NSAID</td>
<td>Non-steroidal anti-inflammatory drugs</td>
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<tr>
<td>OR</td>
<td>Odds Ratio</td>
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<tr>
<td>RI</td>
<td>Resistive Index</td>
</tr>
<tr>
<td>RR</td>
<td>Risk Ratio</td>
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<tr>
<td>SD</td>
<td>Standard deviation</td>
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<tr>
<td>Txb</td>
<td>Transplant kidney biopsy</td>
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Original Papers

This thesis is based on the following papers:


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Summary in Swedish/Sammanfattning på svenska

Perkutana njuromundersökningar har utförts sedan 1944 för att etablera diagnos och behandling. Riskfaktorer som bygger på begränsade data har visat att t.ex. ålder, blodtryck, njurfunktion och nålstorlek är riskfaktorer för biopsikomplikationer. Även om metoderna för biopsitagning har förbättrats under de senaste åren, är det fortfarande en invasiv procedur och allvarliga komplikationer kan inträffa.

Syftet med denna avhandling var att använda större antal data från ett eget nyupptäckt njur- och njurtransplantatbiopsiregister för att utforska riskfaktorer och att försöka att minimerariska risken för patienten och optimera diagnostiken. Ytterligare syfte var att klargöra om olika faktorer (kön, presumptiva diagnoser, lokalisering av biopsier, typ och storlek av biopsinålar) skulle vara till nytta för att reducerera risken för komplikationer efter nativa njuromundersökningar (Nkb) och njurtransplantatbiopsier (Txb). En annan faktor att undersöka var användningen av Resistivt Index (RI) innan utförandet av njurtransplantatbiopsier.

Material och metoder: Ett protokoll för prospektiv multicenter registrering av olika faktorer och komplikationer i samband med Nkb och Txb designades. Data av konsekutiva biopsier från sju sjukhus inkluderades. Alla biopsier, utom en datortomografistyrd Nkb, utfördes med hjälp av ultraljudsledd njuromundersökning med en automatisk "biopsipistol-nål". För biopsier användes 14- till 20- Gauge (G) nålar. Njurfunktionsnivå, det vill säga beräknad GFR (eGFR), beräknades med hjälp av "Modification of Diet in Renal Disease (MDRD) formula" (GFR in mL/min per 1.73m²). För den statistiska analysen användes IBM SPSS Statistik 22 (Armonk, NY, USA) och OpenEpi (Open Source Epidemiologiska Statistik för folkhälsa, www.OpenEpi.com). Data presenteras som Odds Ratio (OR), Risk Ratio (RR) och Konfidensintervall (CI). Ett tvåsidig p-värde på <0,05 ansågs signifikant. Totalt 1299 konsekutiva biopsier (1039 från nativa och 260 från transplanterade njurar) från 1178 patienter (456 kvinnor och 722 män) har utvärderats. Medianåldern för patienterna var 55 år (mellan 16 och 90 år). "Major" (kräver en intervention) och "minor" (ingen behov av intervention) biopsikomplikationer registrerades.

Resultat: Frekvensen av biopsikomplikationer var för Nkb för "overall" 8,8% ("major" 6,7%, "minor" 2,1%) och för Txb "overall" 6,5% ("major" 3,8%, "minor" 2,7%); ingen patient avled. Kvinnor löpte större risk än män att utveckla biopsikomplikationer i Nkb ["major" komplikationer (10,7% versus 4,7%, OR 2,4, CI 1,4-4,2) och "overall" (13,2% versus 6,5%, OR 2,2, CI 1,4-3-5)]. I Nkb, "major" komplikationer var vanligare efter biopsi från höger njure hos kvinnor än hos män (10,8% vs 3,1%, OR 3,7, CI 1,5-9,5), hos patienter med lägre BMI (25,5 vs 27,3, p=0,016) och yngre åldrar (44,8 vs 52,3 år, p=0,002). Lägre medelartäetryck (MAP) i Txb indikerade en risk för "major" komplikationer (90 vs 98 mmHg, p=0,039). Faktorer som antal stick per biopsi och njurfunktion påverkade inte komplikationsfrekvensen. 16 G-biopsinålar jämfört med 18 G gav mer glomeruli per
stick i Nkb (11 vs 8, p<0,001) och Txb (12 vs 8, p<0,001). Sub-analys visade att 18 G 19 mm side-notch biopsinålar i Nkb resulterade i fler ”major” (11,3% vs 3%, OR 4,1, CI 1,4-12,3) och ”overall” komplikationer (12,4% vs 4,8%, OR 2,8, CI 1,1-7,1) hos kvinnor än hos män. Om läkaren hade utfört färre än fyra Nkb per år, var ”minor” (3,5% vs 1,4%, OR 2,6, CI 1,1-6,2) och ”overall” komplikationer (11,5% vs 7,4%, OR 1,6, CI 1,1-2,5) vanligare. Lokaliseringen i njuren där biopsi togs från Nkb och från Txb var inte en riskfaktor för komplikationer. Patienter med IgA-nefrit hade en högre risk för ”major” komplikationer (11,7% vs 6,4%, OR 1,8, CI 1,1-3,2) jämfört med patienter med andra sjukdomar. Fler ”major” komplikationer fanns i Nkb om de hade högre grad av glomeruloskleros (31% vs 20%, p=0,008), medan i Txb om det fanns en högre grad av interstitiell fibros (82% vs 33%, p<0,001). Rebiopsier (Nkb) var vanligare om patienten hade IgA-nefrit (4,7% vs 1,3%, OR 4, CI 1,5-11), var yngre (42,6 vs 52,3 år, p=0,031) eller hade en högre grad av interstitiell fibros (63% vs 34%, p=0,046). Vid Txb, en RI≥0,8 predicerade ökad uppkomst av ”major” (13,3% vs 3,2%, RR 4,2, CI 1,3-14,1) och ”overall” biopsikomplikationer (16,7% vs 5,3%, RR 3,2, CI 1,2-8,6) jämfört med RI<0,8. I gruppen <0,8 korrelerade RI med ålder (r_s=0,28, p<0,001) och systoliskt blodtryck (r_s=0,18, p=0,02). I gruppen ≥0,8 korrelerade RI med graden av interstitiell fibros (r_s=0,65, p=0,006) och systoliskt blodtryck (r_s=0,40, p=0,03). Multipel regressionsanalys visade att i gruppen med RI<0,8 korrelerade RI endast med åldern (p<0,001), medan i gruppen med RI≥0,8 korrelerade RI endast med graden av interstitiell fibros (p=0,003).

**Slutsatser:** De nuvarande resultaten motiverar större uppmärksamhet för ”major” komplikationer efter Nkb hos kvinnor och från deras högra njure, men även hos yngre patienter, och hos dem med lägre BMI; dessutom hos patienter med presumtiv IgA-nefrit och högre grad av glomeruloskleros. Txb-patienter med högre grad av interstitiell fibros har en ökad risk för allvarliga komplikationer. Resultaten indikerar att vid Nkb och Txb bör man helst använda 16 G biopsinålar med 20 mm ”sample size” vilket ger bättre histologisk kvalitet och lägre risk för ”major” komplikationer jämfört med 18 G nålar. Lokaliseringen av biopsitagnings i njuren (Nkb och Txb) förändrar inte komplikationsfrekvensen. Komplikationsrisken för Nkb var lägre om läkaren hade utfört åtminstone fyra biopsier per år. Vid Txb med RI≥0,8 rekommenderas en utökad observation på grund av en större risk för ”major” och ”overall” komplikationer.
Introduction

Kidney diseases are common in general practice. A progressive kidney disease can lead to the need for transplantation or dialysis. To optimize the therapy of the disease, a histological diagnosis achieved by an optimal kidney biopsy is important. To perform a kidney biopsy with minimal risks for complications it is necessary that the performer is trained and has the proper knowledge of follow-up measures. This thesis will deal with risks, quality and safety issues associated with kidney biopsies.

Anatomy of the kidney

The kidneys are located retroperitoneally, just in front of the lower ribs. The left kidney is situated about 2 cm higher than the right kidney. The left kidney lies under the spleen, whereas the right kidney lies under the liver (Figure 1).

Figure 1. Localization of the kidneys, shown from the back.

All arteries, veins, nerves, lymph vessels and the ureter are connected to the hilus of the kidney. The kidneys have an outer cortex containing glomeruli and inner medulla, where the urine is concentrated (Figure 2).

Figure 2. Anatomy of the kidney.

The nephron is the main functional unit of the kidney and its main function is filtering of blood. There are approximately 1,000,000 nephrons per kidney in a healthy person. The nephron consists of glomerular capillaries surrounded by Bowman’s capsule and the tubular system. The blood supply of the glomerulus is delivered by arteria renalis that is divided in five arteriae segmenti and further into arteria interlobaris, arteria arcuata, arteria interlobularis and afferent arterioles (Figure 3) [1].

![Figure 3. Radiography of the kidney visualizing larger vessels at risk such as A. arcuata, A. interlobaris and A. segmentalis.](image)

History of kidney biopsies

In nephrology, biopsies of the native and transplant kidneys have been performed for more than 60 years to establish diagnoses and treatments. The first percutaneous aspiration needle biopsy from the kidney was performed by Nils Alwall in Lund, Sweden in 1944; however he did not publish his results. In the 1950s aspiration biopsies from the kidney were established by Iversen and Brun in Denmark [2-5]. At that time point, the localization of the kidneys was difficult since ultrasound techniques had not yet been introduced in clinical practice, and it was a challenge for the physicians to obtain a kidney biopsy. Intravenous pyelography was used for localization of the kidneys and the patients were biopsied in a sitting position [6]. The percutaneous kidney biopsy technique has improved since the 1950s and in almost all centres real-time ultrasound guidance and an automated spring-loaded biopsy device are currently in use [5, 7]. The biopsy procedure has become more comfortable for the patients since the biopsies can now be performed in a lying position. The first transplant kidney biopsy was performed in 1953 in Paris, France as a peroperative wedge biopsy [8].

Types of biopsy needles

The benefit of achieving enough tissue for conclusive diagnosis has to be weighed against the risk of complications. Existing studies are controversial regarding efficacy and safety of different types (e.g. side-notch and end-cut) and sizes (e.g. 14 to 22 Gauge) of biopsy needles [5, 9-12]. Side-notch biopsy needles cut a “half” core of tissue whereas end-cut needles obtain a “full” core of tissue [9]. The side-notch Tru-cut device is constructed with an inner stylet containing a side-notch and an outer cutting needle (Figure 4 a). The tip of the side-notch biopsy needle is advanced to the kidney capsule and upon firing the inner stylet advances into the kidney (Figure 4 b), the outer cutting needle slides then over the stylet and the biopsy specimen is cut off (Figure 4 c) [9].
Figure 4. Side-notch biopsy needle.

Reprinted from J Vasc Interv Radiol; Volume 21; Constantin A, Brisson ML, Kwan J, Proulx F: Percutaneous US-guided Renal Biopsy: A Retrospective Study Comparing the 16-gauge End-cut and 14-gauge Side-notch Needles, Page No 360, Figure 2, Copyright (2010), with permission from Elsevier.

In the case of end-cut biopsy needles, the entire lumen and almost the whole length of advancement of the needle are used to capture the biopsy specimen. This needle type has a tri-axial design (Figure 5 a). The needle is advanced to the kidney capsule and upon firing the coring needle advances over the stylet (Figure 5 b) and the pincer slides over the coring needle and cuts off the biopsy specimen at the tip (Figure 5 c) [9].
The number of passes needed to obtain sufficient biopsy material should be limited whenever possible.

**Biopsy sample size and needle gauge**

The generally used biopsy needles for kidney biopsies are of sizes 14 to 18 Gauge (G) [5, 13, 14]. A kidney biopsy with non-representative tissue has to be avoided. Therefore the choice of the optimal biopsy needle is important. Table 1 shows the needle sizes and the corresponding biopsy sample sizes [15]. The internal diameter of the biopsy needle is also important for harvesting of an adequate tissue. The size of the normal adult glomerulus is between 200 to 250 µm. The internal diameter of the commonly used biopsy needles differ between 300 to 1000 µm. This means that the internal diameter of an 18 G needle is only a bit larger than a glomerulus [16].
Table 1. Biopsy needle size and corresponding biopsy sample size. Modified from [15].

<table>
<thead>
<tr>
<th>Needle size (Gauge)</th>
<th>Needle outer diameter (mm)</th>
<th>Biopsy cylinder diameter (mm)</th>
<th>Max. cutting area (mm²)</th>
<th>Number of cuts in 3 µM</th>
<th>Number of cuts in 5 µM</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 G</td>
<td>2.0</td>
<td>1.4</td>
<td>14</td>
<td>232</td>
<td>139</td>
</tr>
<tr>
<td>16 G</td>
<td>1.6</td>
<td>1.0</td>
<td>10</td>
<td>165</td>
<td>99</td>
</tr>
<tr>
<td>18 G</td>
<td>1.2</td>
<td>0.7</td>
<td>7</td>
<td>114</td>
<td>68</td>
</tr>
</tbody>
</table>

The number of glomeruli in the biopsy is important for the diagnosis. For transplant kidney biopsies, the Banff 97 Classification requires ten glomeruli and two arteries for a representative biopsy [17]. For native kidney biopsies, there is no accepted international recommendation. Furthermore, the required number of glomeruli in the biopsy sample to diagnose a renal disease is dependent on the type and the glomerular involvement of the disease. There is still controversy regarding the needle size and the histological quality of biopsies required to determine the diagnosis of renal diseases [18]. Some authors recommend that eight or more glomeruli are necessary [19, 20], while others recommend at least twenty [21, 22]. For example, if 20% of glomeruli in the kidney have glomerulosclerosis and five glomeruli are in the biopsy, there exists a 35% probability that all the glomeruli in the biopsy will be normal and the diagnosis will be missed. If 10 or 20 glomeruli are harvested in the biopsy the probability of having only normal glomeruli in the biopsy is reduced to 10%, respectively <1% [22, 23]. However, for the determination of diagnoses such as membranous glomerulonephritis and IgA-nephritis, only one glomerulus can be sufficient [18], and in cases of amyloidosis glomeruli may not be required at all.

As described above the glomeruli are situated in the outer cortex of the kidneys. The number of glomeruli gained by a biopsy is also dependent on the depth of the biopsy needle and the angle of the penetration of the biopsy needle. If the biopsy needle penetrates too deep through the cortex into the medulla, the tissue will mainly originate from the medulla where only few or no glomeruli are present. Furthermore
the deep penetration of the biopsy needle can lead to damage of the blood vessels causing bleeding complications. Therefore a tangential approach of the biopsy needle to the cortex is the optimal choice to perform kidney biopsies [24, 25].

**Biopsy methods**

In addition to percutaneous kidney biopsies, as described in this thesis, to reduce the risk for biopsy complications there are other kinds of biopsy methods available with absolute and relative contraindications.

*The transjugular renal biopsy* is performed in an angiography suite. By ultrasound guidance an internal jugular vein puncture is performed. The right internal jugular vein is preferred because of the direct access to the inferior vena cava. The sheath is advanced over a stiff guide wire into the inferior vena cava. Then the renal vein is catheterized and a peripheral position will be located. The biopsy needle is then inserted and a spring-loaded gun obtains tissue samples. The advantage of this type of biopsy is that it is safer since possible bleedings end up inside veins, and possible capsular perforation can be managed directly by elective coil embolization [6, 26-28].

*Open and laparoscopic kidney biopsies* are other options. These biopsies are performed under general anaesthesia and direct vision. The advantages are better identification of kidneys and that homeostasis can easily be achieved; while the disadvantages are the general anaesthesia and the surgical procedure [6, 26-28].

*The transurethral renal biopsy* is a special kind of biopsy method that is seldom used. In this case a biopsy needle is introduced via cystoscopy [6, 28].

**Indications and contraindications for kidney biopsies**

The clinical indications for performing native kidney biopsies are proteinuria, microscopic or macroscopic haematuria, acute renal failure of unknown origin and suspicion of glomerulonephritis, renal parenchymal disease or vasculitis. Studies have shown that the histological diagnosis in native kidney biopsy is different from the clinical assumed diagnosis in 50% to 60% of cases, and the treatment is altered in up to 80% of cases dependent on the diagnosis obtained via biopsies [23, 29, 30].

The diagnoses of rejection, chronic allograft nephropathy, recurrent disease and the monitoring of immunosuppressive therapy are clinical indications for transplant kidney biopsies [2, 6]. Furthermore, protocol biopsies of renal allografts are
performed to examine the effect of different immunosuppressive drug therapies and to evaluate histological changes in the kidney transplant over time [16, 31-33].

The classical contraindications for a kidney biopsy can be divided in absolute and relative. Absolute contraindications are small kidneys bilaterally, coagulopathy or severe hypertension, whereas relative contraindications are a solitary kidney, uncooperative patient, multiple bilateral renal cysts, pregnancy and the inability of the patient to lie flat on a bed [6, 27, 28]. Biopsy should be avoided in the course of treatment for a pyelonephritis or perinephric abscess. If acute biopsy is required for adequate diagnoses in such cases adequate antibiotic therapy should be used to avoid blood spread of bacteria and secondary abscesses.

Definition of biopsy complications (“major” and “minor” complications)

There are different definitions of major and minor biopsy complications in the literature, which makes it difficult to compare the frequency of the complications between studies. In this thesis the criteria for biopsy complications according to Whittier et al. [34, 35] were used. Adverse effects after native and transplant kidney biopsies can be divided into major and minor complications (Table 2). Major complications, such as bleeding requiring blood transfusion, acute renal obstruction, and septicaemia, all require an intervention (e.g. blood transfusion, invasive procedure - radiological/surgical/urological, or antibiotic treatment); another major complication is death. Minor complications (e.g. gross haematuria) resolve spontaneously without the need for intervention [34, 35]. Minor side-effects are microscopic haematuria (seen in nearly all cases) or asymptomatic perinephric hematoma (up to 90% of cases) [35, 36]. Another biopsy complication is the development of an arteriovenous fistula, which is caused by damage to the wall of a blood vessel. If the fistula causes symptoms, a radiological (e.g. coil embolization) or surgical intervention may be required [35].
Table 2: Major and minor biopsy complications in native and transplant kidney biopsies.

<table>
<thead>
<tr>
<th>Major complications</th>
<th>Minor complications</th>
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<tbody>
<tr>
<td><strong>Bleeding complications:</strong></td>
<td><strong>Bleeding complications:</strong></td>
</tr>
<tr>
<td>- bleeding requiring blood transfusion</td>
<td>- gross haematuria</td>
</tr>
<tr>
<td>- congestion of urinary tract/hydronephrosis/urinary bladder tamponade because of bleeding</td>
<td>- perinephric hematoma without symptoms</td>
</tr>
<tr>
<td>- clinically significant hematoma (extended hospital care and treatment for pain)</td>
<td></td>
</tr>
<tr>
<td>- extended care because of gross haematuria (prolonged observation, intravenous fluid replacement)</td>
<td></td>
</tr>
<tr>
<td><strong>Others:</strong></td>
<td><strong>Others:</strong></td>
</tr>
<tr>
<td>- infection requiring antibiotic treatment</td>
<td>- fall in blood pressure without treatment</td>
</tr>
<tr>
<td>- fall in blood pressure requiring treatment</td>
<td>- arteriovenous fistula without symptoms</td>
</tr>
<tr>
<td>- perforation of the small intestine with peritonitis, requiring blood transfusion and surgery</td>
<td></td>
</tr>
<tr>
<td>- extended care because of fever after biopsy</td>
<td></td>
</tr>
<tr>
<td>- arteriovenous fistula requiring an intervention</td>
<td></td>
</tr>
<tr>
<td><strong>Damage to other organs during the biopsy</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Nephrectomy after biopsy</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Any invasive radiological/urological/surgical treatment related to biopsy complications</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td></td>
</tr>
</tbody>
</table>
Type of biopsy complications and risk factors for kidney biopsies

The frequency of major complications differs among clinical studies and is dependent on factors such as the techniques used (manual/automated biopsy needles, needle size, number of passes, etc.). In native kidney biopsies, the frequency of major complications is in the range of 1–7%, and minor complications in the range of 6.6–19.7% [7, 34, 37-42]. Death is very uncommon today, but has been observed in 0.1% of native kidney biopsies [34]. In transplant kidney biopsies, the frequency of major (0.4–2.9%) and minor complications (about 6%) is lower compared to native kidney biopsies. Most of the studies are on protocol biopsies [31, 33, 39, 43].

The risk factors for complications after native and transplant kidney biopsies are not completely known. Previous studies have shown that, e.g. higher age, high blood pressure, low kidney function, larger biopsy needle size, low level of haemoglobin and thrombocytes are risk factors for complications in native kidney biopsies [7, 34, 44-48]. However, different studies showed varying results about risk factors for biopsy complications depending on the study design. In transplant kidney biopsies, a study by Morgan et al. [49] found that the “major” biopsy complication rate among “cause” (because of renal transplant dysfunction) compared protocol biopsies (as part of post transplant management to screen for early rejection) were significantly higher (2.7% versus 0.33%). A further study showed that biopsies performed within 1 week of transplant had a 311% higher risk for developing biopsy complications, and that post biopsy reductions in haematocrit and haemoglobin at 4 hours were associated with biopsy complications [50]. No consensus about risk factors for kidney biopsy complications exists as of yet. Although the techniques of the percutaneous native and transplant kidney biopsy have improved, it is still an invasive procedure and complications do occur.

Whether protocol transplant kidney biopsies should be performed routinely is still debated [51] with some studies recommending protocol transplant kidney biopsies [52], whereas others do not [53].

Outpatient and inpatient biopsies

In Sweden as well as in other countries, it is common practice to perform native kidney biopsies in the inpatient setting, i.e. the patients stay at least 24 hours at the hospital for observation after biopsy. However, the transplant kidney biopsies are performed as inpatient or outpatient since the transplant kidneys are more superficially located, and do not follow the respiratory movement, which makes it easier to perform biopsies. Further, it is also easier to detect such biopsy complications [54].
The observation period after outpatient biopsy varies. After a transplant kidney biopsy some suggest that patients may be discharged after four hours of observation [31, 33]. A six-hour observation period was investigated by two groups. Jiang et al. [40] examined 475 native and transplant kidney biopsies performed in an outpatient setting with an observation period of 6 hours. The complication rate was 8.2% for overall, 6.9% for minor and 1.3% for major biopsy complications. Lin et al. [55] compared 147 inpatient and 183 outpatient native kidney biopsies. They found no significant differences in the frequency of biopsy complications between the inpatient versus outpatient biopsies.

Eight hours of observation was recommended by Yablon et al. [54]. They found that a minimum of 8 hours of observation after transplant kidney biopsy should be recommended since all but one complication occurred within this time period and they stated that an overnight observation may still be the safest. An observational study in 3738 transplant kidney biopsies [50] reported that most complications occurred within 4 hours post biopsy period, although severe complications were often delayed with 67% of these occurring more than 8 hours after the biopsy (mean time 12 h 22 min).

Other authors [56, 57] recommend performing outpatient native kidney biopsies only in “low-risk patients”. Such “low-risk” is, however, defined differently. For example, in the study by Golay et al. [56] “low-risk patients” are younger (10-60 years), BMI≤30 kg/m², blood pressure <150/100 mmHg, serum creatinine ≤3 mg/dL, platelet count >150000/mm³ with normal coagulation profile, no ongoing anticoagulation and live nearby the hospital (within 2 hours). McMahon et al. [57] defined “low-risk patients” as patients with systolic blood pressure <140 mmHg, BMI<35 kg/m², platelet ≥50000/mm³, no ongoing anticoagulation and no liver disease.

On the other hand there are studies stating that native kidney biopsies should be performed as an inpatient setting to improve patient’s safety due to the delay of developing complications after biopsies. A study of native kidney biopsies in 750 patients [34] showed that 42% of all complications were detected by ≤4 hours, 67% by ≤8 hours, 85% by ≤12 hours, 89% by ≤24 hours and 11% by >24 hours. Major complications in this study were identified in 38% by ≤4 hours, 67% by ≤8 hours, 89% by ≤12 hours, 91% by ≤24 hours and 9% by >24 hours. Thus, the authors stated that an optimal observation time after biopsies should be up to 24 hours and that there is a risk of missing ≥33% of complications when using an observation time of ≤8 hours. Marwah et al. [58] found that 77% of all complications were identified by 8 hours observation period and at 24 hours 98% of all complications and 100% of major complications were detected.
There are currently no predictors for biopsy complications. Neither an examination by ultrasound after biopsies to detect a perinephric hematoma nor changes in haematocrit or haemoglobin before and after biopsies are reliable predictors for biopsy complications [34, 37].

Thus, it is still controversial to perform native kidney biopsies in an outpatient setting. To further clarify this issue there is a need for large prospective studies in this field.

The strict bed rest of patients after biopsies is 2 to 12 hours in different studies and no consensus exists [59].

**Antiplatelet drugs and kidney biopsies**

The discontinuation of antiplatelet and non-steroidal anti-inflammatory drugs 5 to 7 days before performing renal biopsies to reduce the risk of bleeding is widespread. However, there are studies that have shown that the ongoing treatment with antiplatelet drugs does not alter the major biopsy complication rate. A retrospective study of 1120 native kidney biopsies by Mackinnon et al. [60] showed that the risk for major biopsy complications was not reduced after stopping antiplatelet drugs (acetylsalicylic acid and clopidogrel) before performing the biopsies; whereas the risk for minor biopsy complications was reduced. A further retrospective study [61] examined the influence of aspirin (acetylsalicylic acid) on the incidence of bleeding in 15 181 percutaneous biopsies, including 5832 kidney biopsies (native and transplant), and found that the incidence of bleeding in patients with aspirin treatment was not different compared to patients without aspirin. In the transplant kidney setting, treatment with acetylsalicylic acid is usually uninterrupted [5, 33]. However, the discontinuation of antiplatelet drugs can increase the risk of thrombotic vascular events.

**Bleeding time and desmopressin in kidney biopsies**

In patients with uraemia, the administration of desmopressin (1-deamino-8-D-arginine vasopressin [DDAVP], Octostim®) is generally used to decrease the prolonged bleeding time and to improve haemostasis [28]. The measurement of bleeding time is still controversial because it is not standardized (insensitive, operator-dependent, difficult to reproduce) [62, 63]. The importance of prolonged bleeding time for the complications in kidney biopsies and the administration of desmopressin are unclear. The risk for bleeding complications is probably still higher for patients after treatment of prolonged bleeding time with desmopressin compared to the patients who have had a normal bleeding time before the biopsy.
[34, 62, 64-66]. Some authors recommend desmopressin treatment before biopsies [67] while others are critical to this treatment [66]. Therefore the administration of desmopressin remains debatable.

**Resistive Index**

For measurement of renal blood flow in kidneys, the Resistive Index (RI) is clinically used [68]. In transplant kidney biopsies, studies have found that the RI is a predictor for renal allograft survival and patient death [69-71].

The RI is calculated by ultrasound as $RI = (\text{peak systolic velocity} - \text{end-diastolic velocity})/\text{peak systolic velocity}$. It is usually measured in three to five different locations of the arcuate arteries (at the corticomedullary junction) or interlobar arteries (adjacent to medullary pyramids), and the mean of these RIs is calculated. Studies have shown that a normal RI is 0.6 to 0.7, but in elderly patients without renal disease the normal RI can exceed 0.7 [68].

The RI in transplant kidneys is usually performed as a clinical routine examination to detect dysfunction of the kidney transplant, such as rejection. An elevated RI was previously considered as a marker for rejection, but newer studies have shown a lack of specificity of an elevated RI in transplant kidneys. Although the RI is not a specific marker, it can be used to detect vascular complications in the transplant kidney [68].
Renal pathology

The main cause for impaired kidney function in younger patients is glomerulonephritis. In membranous glomerulonephritis, minimal change disease, focal segmental glomerulosclerosis (FSGS) and membranoproliferative glomerulonephritis, the podocytes (the epithelial cells outside the glomerular capillaries) are mainly damaged, and this results in potent proteinuria (Figure 6). However, in IgA-nephritis the mesangium is typically affected (Figure 7 a and b) and the damage results in microscopic haematuria and moderate proteinuria [72].

IgA-nephritis and Henoch-Schönlein-nephritis are considered to be related diseases and show identical pathological and biological abnormalities. But there are some differences. IgA-nephritis is usually diagnosed in patients between 15 and 30 years of age whereas Henoch-Schönlein-nephritis is mainly seen in children. Nephritic and/or nephrotic syndromes occur more often in Henoch-Schönlein-nephritis compared to IgA-nephritis. Further, Henoch-Schönlein-nephritis shows extrarenal clinical signs, such as purpura, arthritis and abdominal pain [73].

Figure 6. Nephrosis. Subepithelial immune complexes and/or podocyte damage causes generalized capillary protein leakage and marked proteinuria. No or minimal haematuria is seen.
Illustration by Johan Mölne.
Figure 7 a. IgA-nephritis with mesangial proliferation.
Photo courtesy of Johan Mölne.

Figure 7 b. IgA-nephritis (Immunoperoxidase). IgA deposits are mainly seen in the mesangium (brown staining).
Photo courtesy of Johan Mölne.
Figure 8. Nephritis. Endothelial damage and/or subendothelial immune complexes leads to inflammation and capillary wall damage causing leakage of red blood cells but low amount of proteinuria. Illustration by Johan Mölne.

Further, there are different types of vasculitis (granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)) and SLE-nephritis (systemic lupus erythematosus). In these diseases, the endothelial cells are damaged due to immune deposits leading to inflammation and capillary destruction and the patients suffer mainly from haematuria and rapid damage of the kidney tissue (Figure 8). These types of glomerulonephritis can also occur secondary to inflammatory system diseases, infections, cancer and drugs [74].

The different types of glomerulonephritis and their characteristics and clinical syndromes are illustrated in Table 3 [15, 72, 74].
Table 3. Types of glomerulonephritis and their characteristics. Modified from [15, 72, 74].

<table>
<thead>
<tr>
<th>Type of glomerulonephritis (GN)</th>
<th>Manifestation in the kidney</th>
<th>Clinical syndrome</th>
<th>Light microscopic findings in the biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Membranous GN</td>
<td>Epithelial</td>
<td>Nephrotic syndrome</td>
<td>Altered capillary walls and uneven/thickened basal membrane</td>
</tr>
<tr>
<td>Minimal change GN</td>
<td>Epithelial</td>
<td>Nephrotic syndrome</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Electron microscopy detects effacement of podocyte foot processes.)</td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis</td>
<td>Epithelial</td>
<td>Nephrotic syndrome</td>
<td>Sclerosis in some glomeruli and only in a segment of each glomeruli</td>
</tr>
<tr>
<td>Membranoproliferative GN</td>
<td>Mixed</td>
<td>Nephrotic syndrome and/or chronic GN</td>
<td>Increased number of cells and altered capillary walls</td>
</tr>
<tr>
<td>Endocapillary GN (often postinfectious)</td>
<td>Endothelial</td>
<td>Acute GN</td>
<td>Increased number of cells in glomerular capillaries, often granulocytes</td>
</tr>
<tr>
<td>Extracapillary GN (Crescentnephritis, often secondary)</td>
<td>Endothelial</td>
<td>Rapidly progressive GN</td>
<td>Necrosis and “crescents” in glomeruli</td>
</tr>
<tr>
<td>IgA-nephritis</td>
<td>Mesangial</td>
<td>Pathological urine samples without symptoms (microscopic haematuria, proteinuria) or macroscopic haematuria or chronic GN</td>
<td>Increased number of mesangial cells</td>
</tr>
</tbody>
</table>
As described in the “Introduction” there are many options to perform a kidney biopsy. The present recommendations only give sparse information and are based on limited amount of data. Differences in biopsy techniques between centres exist in Sweden. Still many questions remain: Is there nowadays still a risk for severe biopsy complications? If so what is the main reason and can they be prevented or at least limited? What about conventional factors such as blood pressure and kidney function? Can the histological finding anticipated help to be more cautious about biopsy complications? Does gender have any importance? Is there any benefit using ultrasound and Resistive Index?
Aims

The general aims of this thesis were to study biopsy complications and risk factors in native and transplant kidney biopsies to improve the patient’s safety and the biopsy quality. Further aims were to examine if specific renal diseases and biopsy techniques are correlated to biopsy complications and how the risk for re-biopsies can be reduced.

The specific aims of the studies were:

Study I

The aims of study I were to clarify the biopsy complications and risk factors for biopsy complications in native and transplant kidney biopsies to improve patients’ safety.

Study II

The aims of study II were to examine the quality and safety of different types and sizes of biopsy needles used in native and transplant kidney biopsies.

Study III

The aim of study III was to investigate if specific renal diseases and histological findings can be related to biopsy complications.

Study IV

The aim of study IV was to investigate if Resistive Index could be a useful predictor for complications after kidney transplant biopsies.
Materials and Methods

A protocol for prospective registration of clinical parameters and complications associated with native and transplant kidney biopsies was designed (Figure 9) with the intention to achieve a registry for quality assessment, and to build up a national kidney biopsy registry. Data of biopsies and their procedures and patients´ demography were consecutively added into the registry during the whole study period.

The protocol was used prospectively at all medical centres in western Sweden (six centres, including one university hospital), and retrospectively and prospectively at one medical centre (university hospital) in northern Sweden.

The following medical centres, hospitals and organisations in Sweden participated in our study:

- Skaraborg Hospital, Skövde (Departments of Nephrology and Radiology)
- Umeå University Hospital, Umeå (Departments of Public Health and Clinical Medicine and Radiology)
- Sahlgrenska University Hospital, Gothenburg (Departments of Nephrology, Pathology and Radiology)
- Transplantation Centre, Sahlgrenska University Hospital, Gothenburg
- Northern Älvsborg County Hospital, Trollhättan (Department of Nephrology)
- Southern Älvsborg Hospital, Borås (Departments of Nephrology and Radiology)
- Halland Hospital, Halmstad (Departments of Nephrology and Radiology)
- Sektorsrådet för Njurmedicin, Västra Götalands Region
Figure 9: Protocol for registration of clinical complications (translated into English).
The Regional Ethical Review Board in Gothenburg/Sweden approved all studies (DNR: 701-08, EXP 2008-12-18; DNR: T586-14, 701-08, EXP 2014-07-15).

The collected data included in the protocol are shown in Figure 9. Some parts of this protocol are the basis for the Swedish Biopsy Registry which is part of SNR (Svenskt Njurregister, Swedish Renal Registry). In addition to these data, information was included regarding the experience (specialist, trainee) of the physician carrying out the biopsy. Data were included for centres performing investigation with the Resistive Index in transplant kidney biopsies.

Furthermore, the protocol requested information about complications with the following alternatives: fall in blood pressure requiring treatment, congestion of the urinary tract, urinary bladder tamponade, infection requiring antibiotic treatment, clinically significant hematoma, bleeding requiring blood transfusion, surgical intervention after biopsy, damage to other organs during the biopsy, gross haematuria after biopsy, nephrectomy after biopsy, extended care because of complications, and a free comment field (Figure 9).

All native and transplant kidney biopsies in our studies, except one native kidney biopsy performed by computer tomography-guidance, were performed using real-time ultrasound guidance (i.e. an ultrasound machine Logiq E9 with 2–5 MHz-sector transducer [GE Healthcare, Chalfont St Giles, UK] or similar) and an automated spring-loaded biopsy device. For native and transplant kidney biopsies, 16- and 18-gauge needles were used. In addition, three native kidney biopsies were performed using 14- and 20-gauge needles. The maximum length of biopsy specimens that can be achieved with a 16 G side-notch needle (according to the specifications of the manufacturers) is either 19 mm (Magnum and Max-Core by BARD Medical, Covington, GA, USA) or 20 mm (HTR 16/15 by Tsunami Medical, San Possidonio, Italy). For 18 G needles the maximum specimen length is 19 mm for side-notch (Magnum by BARD Medical, Covington, GA, USA) versus 19 mm and 29 mm for end-cut needles (BioPince by Angiotech, Vancouver, BC, Canada).

Radiologists performed the biopsies, except for one centre where nephrologists did the biopsies. In the case of native kidney biopsies performed by nephrologists, an ultrasonographer localized the kidneys and the nephrologist performed the biopsies via real-time ultrasound guidance. For the transplant kidney biopsies taken by nephrologists, the nephrologists themselves localized the transplant kidney and performed the biopsies using real-time ultrasound guidance.

Before biopsies were performed, basic investigations such as blood pressure (systolic and diastolic), pulse, temperature, weight, length, electrocardiography, complete blood count (haemoglobin, platelets, leukocytes, haematocrit), renal function panel (sodium, potassium, calcium, albumin, phosphate, blood urea...
nitrogen, serum creatinine), hepatic status (ALT, AST, ALP, serum bilirubin), serum bicarbonate, CRP, ESR, bleeding parameter (prothrombin time [INR], activated partial thromboplastin time [aPTT]), blood group, blood sugar level, and urine samples (urine test strip, light microscopy of the urine samples) were obtained from all patients.

The bleeding time was measured at two centres during the beginning of this study and before the native kidney biopsies were performed. Later during the study period these centres stopped using this measurement.

If the blood pressure was above 160/90 mmHg, extra antihypertensive drugs (e.g. nifedipine) were administered. In one centre, if serum creatinine was higher than 150 μmol/l, desmopressin (Octostim®) was administered subcutaneously (0.3μg/kg body weight) before biopsying native and transplant kidneys. In the other centres, desmopressin was only used if a known bleeding disorder existed and/or bleeding time was elevated. Dependent on the hospital, the patients were treated with paracetamol, opioid analgesic (ketobemidone or morphine) subcutaneous or/and benzodiazepine (flunitrazepam or diazepam) before the biopsies. The treatment with anticoagulants (acetylsalicylic acid, clopidogrel and warfarin) was stopped seven days and NSAID-treatment three days before native and transplant kidney biopsies. One centre performed the transplant kidney biopsies even if the patient was taking acetylsalicylic acid.

The patients were instructed to fast for four hours before the biopsy. Patients having native kidney biopsies were turned on the side opposite to the biopsied kidney with a pillow under the flank; whereas patients having transplant kidney biopsies were in the supine position.

Before performing each biopsy, the patient had a diagnostic renal ultrasound examination (bilateral for native kidneys) to evaluate the length and depth of the kidney, anatomical abnormalities, and to clarify to avoid the presence of hydronephrosis. The skin over the kidney was sterilized with an antiseptic solution. Next the skin and the subcutaneous tissue was infiltrated with 10 mL xylocaine 10 mg/ml. The local anaesthetic was injected down to and including the renal capsule as guided using real-time ultrasound. An incision was made with a scalpel blade (No. 11) and the automated biopsy needle inserted into the renal cortex under real-time ultrasound guidance. No microscopic control of the obtained specimens was performed. The biopsy specimens were placed in a formalin-type fixative (buffered paraformaldehyde, pH 7.4, HistoLab AB, Västra Frölunda, Sweden) and sent to either of two renal pathology laboratories and examined by a total of four pathologists. The following parameters were registered: histological diagnosis, number of glomeruli per biopsy, the degree of glomerulosclerosis and interstitial fibrosis (in 10 % intervals by visual assessment) [75], and the total length of biopsy
specimens in mm (adding the length of all pieces, excluding kidney capsule and extra renal connective tissue). Light microscopy, immunohistochemistry (immunoperoxidase or immunofluorescence) and electron microscopy were used to establish a histological diagnosis.

All native kidney biopsies were performed as inpatient procedures. The transplant kidney biopsies were performed as either outpatient or inpatient procedures. After an inpatient biopsy the patient stayed in bed for four hours; the first hour lying on the side of the biopsied native kidney or in the supine position for patients who had transplant kidney biopsies. Blood pressure (systolic and diastolic), pulse, vital signs, and visual analogue scale (VAS) for pain were measured every 15 min for the first hour, every 30 min for the second hour, and every 60 min for a further three hours. Patients who had outpatient transplant kidney biopsies were discharged after an observation period of two hours of bed rest (blood pressure and pulse were measured every 15 min for the first hour and every 30 min for the second hour), and after a check of their haemoglobin levels. Patients biopsied at the inpatient ward stayed overnight for observation.

The kidney function level, i.e. estimated GFR (eGFR), was calculated using the Modification of Diet in Renal Disease (MDRD) formula (GFR in ml/min per 1.73m²) [76].

For statistical analyses the IBM SPSS Statistic 22 (Armonk, NY, USA) and OpenEpi (Open Source Epidemiologic Statistics for Public Health, www.OpenEpi.com) were used. Fisher’s exact test and χ² analyses were used for the cross-tabulation of data. Independent t-test and Mann–Whitney U test were used. Correlation analyses were performed by Pearson’s (r) and Spearman’s test (rₛ). Multiple regression analyses were performed using Stepwise analysis. Data are presented as Odds Ratio (OR), Risk Ratio (RR) and Confidence Intervals (CI). For parametric analyses mean values ±1 standard deviation are presented and for non-parametric analyses the median and range are presented. A two sided p-value of <0.05 was considered significant.

This thesis has used patients´ data which have been registered in a kidney biopsy registry that was started in 2006, and the registration of such patients is still ongoing.
Study I

In the registry, a total of 1001 consecutive biopsies in 917 patients (352 women and 565 men) had been included. The median age of patients was 54 years (range 16–90 years). The registry contained data concerning 826 native and 175 transplant kidney biopsies. The data were collected from January 1, 2006 to March 27, 2013.

Study II

A total of 1299 consecutively performed biopsies in 1178 patients (456 women and 722 men) were included in the registry. The median age of patients was 55 years (range 16-90 years). In total 1039 biopsies were taken from native kidneys and 260 from transplant kidneys. Data were collected from January 1, 2006 to April 15, 2014.

Study III

A total of 1081 consecutive biopsies from 994 patients (383 women and 611 men) were included in the registry. The median age of patients was 54.5 years (range 16–90 years). In total 896 biopsies were taken from native kidneys and 185 from transplant kidneys. The data were collected from January 1, 2006 until August 28, 2013.

Study IV

A total of 220 consecutive transplant kidney biopsies in 175 patients (68 women and 107 men) were prospectively included in the registry. The median age of patients was 55.5 years (range 18-82 years). The Resistive Index (RI) was calculated just before the biopsy procedure in all biopsies. Data were collected from four medical centres that included two university hospitals from September 14, 2007 until February 6, 2015.
Results

In native kidney biopsies, the frequency of biopsy complications was 9.1% for overall, 7% for major, and 2.1% for minor complications. The complication frequency in transplant kidney biopsies was 6.9% for overall, 4% for major complications, and 2.9% for minor complications (Figure 10) [77] [Study I].

![Frequency of complications](image)

Figure 10. Frequency of biopsy complications.

There was a higher risk of major (9.6% versus 4.5%, OR 2.2, CI 1.3–3.7) and overall complications (12.2% versus 6.5%, OR 2.0, CI 1.3–3.1) after native and transplant kidney biopsies for women than for men [77] [Study I]. Women had a higher risk for development of major (10.7% versus 4.7%, OR 2.4, CI 1.4–4.2) and overall biopsy complications (13.2% versus 6.5%, OR 2.2, CI 1.4-3.5) compared to men in native kidney biopsies (Figure 11).
Figure 11. Frequency of biopsy complications in women and men in native kidney biopsies.

Major complications were more frequent in biopsies taken from the right kidney in women than in men (10.8% versus 3.1%, OR 3.7, CI 1.5–9.5). In native kidney biopsies, lower BMI was a risk factor for both major (BMI 25.5 versus 27.3, p=0.016) and overall complications (BMI 25.8 versus 27.3, p=0.022) (Figure 12). Also younger age was a risk factor for both major (44.8 versus 52.3 years, p=0.002) and overall (47 versus 52.3 years, p=0.015) complications (Figure 13) [77] [Study I].

Figure 12. Mean BMI and biopsy complications in native kidney biopsies.
Figure 13. Mean Age and biopsy complications in native kidney biopsies.

In transplant kidney biopsies, lower mean arterial pressure (MAP) was a risk factor for major complications (MAP 90 versus 98 mmHg, p=0.039) and for overall complications (MAP 92 versus 98 mmHg, p=0.04). Diastolic blood pressure, number of passes, kidney function, number and specialty of the physicians who performed the biopsies per centre were not risk factors for complications either in native or in transplant kidney biopsies. The multi-regression analyses showed that younger age (p=0.005), female sex (p=0.002), and lower BMI (p=0.043) were risk factors for major complications in native kidney biopsies and only younger age was a risk factor for minor complications (p=0.008) for transplant kidney biopsies [77][Study I].

In native kidney biopsies 16 G needles compared to 18 G obtained more glomeruli per pass (G/P) (11 versus 8, p<0.001) and more glomeruli per length of biopsy specimen (glomeruli per mm) (G/L) (1.2 versus 0.9, p<0.001). In transplant kidney biopsies, 16 G needles with sample size 20 mm, compared to 18 G needles with 19 mm sample size, resulted in more G/P (12 versus 8, p<0.001), G/L (0.9 versus 0.74, p=0.028) and length of biopsy specimen per pass (mm) (L/P) (14.6 versus 11.9, p<0.001) [78][Study II].
In native kidney biopsies taken by side-notch needles of 18 G and 19 mm, but not end-cut needles, women suffered more major (11.3% versus 3%, OR 4.1, CI 1.4-12.3) and overall complications (12.4% versus 4.8%, OR 2.8, CI 1.1-7.1) than men (Figure 14) [78] [Study II].

![Frequency of complications](image)

Figure 14. Frequency of biopsy complications in native kidney biopsies using an 18 G side-notch needle with 19 mm sample size.

The localization within the kidney of the native and transplant kidney biopsies was not a risk factor for biopsy complications or for biopsy quality. Physicians who had performed less than 30 native kidney biopsies during the study period of 8.3 years (compared to performing more than 30) had more minor (3.5% versus 1.4%, OR 2.6, CI 1.1-6.2) and overall complications (11.5% versus 7.4%, OR 1.6, CI 1.1-2.5) (Figure 15). In transplant kidney biopsies, such comparable results were not found [78] [Study II].
Figure 15: Biopsy complications and biopsies per performer.

The most common renal diagnosis obtained after biopsy was IgA-nephritis (14.3%) in native kidney biopsies; and in transplant kidney biopsies rejection was most common (21.1%). A higher degree of glomerulosclerosis (31% versus 20%, p=0.008) was a risk factor for major biopsy complications in native kidney biopsies; whereas in transplant kidneys a higher degree of interstitial fibrosis (82% versus 33%, p<0.001) was associated with major biopsy complications. Furthermore, IgA-nephritis was a risk factor for major complications compared to all other diagnoses (11.7% versus 6.4%, OR 1.8, CI 1.1–3.2). Patients with Henoch-Schönlein-nephritis did not suffer from more biopsy complications compared to other diagnoses. However, the number of cases was small. None of the other diseases including amyloidosis were associated with major biopsy complications [79] [Study III].

Native kidney biopsies

The degree of glomerulosclerosis correlated positively to age (r=0.118, p=0.001), systolic (r=0.132, p<0.001) and diastolic (r=0.119, p<0.001) blood pressure, MAP (r=0.117, p=0.002), serum creatinine (r=0.194, p<0.001), degree of interstitial fibrosis (r=0.632, p<0.001), and correlated inversely to eGFR (r=−0.365, p<0.001). The degree of interstitial fibrosis correlated positively to age (r=0.241, p=0.003), systolic (r=0.327, p<0.001) and diastolic (r=0.190, p=0.021) blood pressure, MAP (r=0.282, p=0.001), serum creatinine (r=0.696, p<0.001), weight (r=0.199, p=0.016),
BMI \( (r=0.184, \ p=0.025) \), and degree of glomerulosclerosis \( (r=0.632, \ p<0.001) \), and correlated inversely to eGFR \( (r=-0.680, \ p<0.001) \).

**Transplant kidney biopsies**

The degree of *glomerulosclerosis* correlated positively with the degree of interstitial fibrosis \( (r=0.436, \ p<0.001) \). The extent of *interstitial fibrosis* correlated positively with serum creatinine \( (r=0.364, \ p<0.001) \), body weight \( (r=0.286, \ p=0.005) \) and degree of glomerulosclerosis \( (r=0.436, \ p<0.001) \), and inversely to eGFR \( (r=-0.253, \ p=0.013) \).

In non-diagnostic biopsies in native kidneys \( (n=17) \), the number of glomeruli were fewer (mean of 1 versus 22, \( p<0.001 \)), age did not differ (Figure 16) and the biopsy specimens were shorter (11.5 mm versus 21 mm, \( p=0.034 \)) than in adequate biopsies. At least two glomeruli per biopsy were needed to establish a histological diagnosis, except in case of amyloidosis which can be diagnosed without reference to glomeruli. Non-diagnostic versus diagnostic native kidney biopsies showed no difference in gender, age, blood pressure, number of passes, degree of glomerulosclerosis, kidney function or BMI. The amount of interstitial fibrosis could not be estimated in these biopsies due to lack of sufficient amounts of cortex [79] [Study III].

The risk of re-biopsies (since the first biopsies were non-diagnostic) was higher in younger patients (42.6 versus 52.3 years, \( p=0.031 \)), in patients with IgA-nephritis (4.7% versus 1.3%, OR 4, CI 1.5-11) and in patients with a higher degree of interstitial fibrosis (63% versus 34%, \( p=0.046 \)) [79] [Study III].

![Figure 16. Relation between glomeruli and age in non-diagnostic native kidney biopsies.](image)
A Resistive Index (RI) in the transplant kidney of ≥0.8, verified just before the biopsy, was found as a predictor for major and overall biopsy complications. Patients with RI≥0.8 had more major (13.3% versus 3.2%, RR 4.2, CI 1.3-14.1) and overall complications (16.7% versus 5.3%, RR 3.2, CI 1.2-8.6) compared to patients with RI<0.8. Binary logistic regression analysis was performed including biopsy complications (major, minor and overall complications) as dependent factor and as variables age, gender, systolic and diastolic blood pressure, BMI, RI≥0.8 and <0.8. The only significant variable in this model was RI≥0.8 for major (p=0.007) and for overall complications (p=0.015) [Study IV].

RI correlated positively to age (r_s=0.27, p<0.001), systolic blood pressure (r_s=0.13, p=0.049), and BMI (r_s=0.15, p=0.027), and inversely to eGFR (r_s=-0.15, p=0.03) and diastolic blood pressure (r_s=-0.14, p=0.047). In the <0.8 group, RI correlated with age (r_s=0.28, p<0.001) and systolic blood pressure (r_s=0.18, p=0.02) (Figure 17). In the ≥0.8 group, RI correlated with the degree of interstitial fibrosis (r_s=0.65, p=0.006) and systolic blood pressure (r_s=0.40, p=0.03) (Figure 18) [Study IV].
Figure 17: Correlation between Resistive Index (RI) <0.8 and clinical variables.
Figure 18: Correlation between Resistive Index (RI) $\geq 0.8$ and clinical variables.
In total 1299 consecutive biopsies (1039 native and 260 transplant kidneys) in 1178 patients (456 women and 722 men) were used for investigation in this thesis. The median age of patients was 55 years (range 16-90 years). The frequency of biopsy complications for native kidney biopsies was overall 8.8% (major 6.7%, minor 2.1%), and for transplant kidney biopsies was overall 6.5% (major 3.8%, minor 2.7%).

There were no differences in the frequency of biopsy complications neither in native nor in transplant kidney biopsies between all centres for all studies performed in this thesis.
Discussion

Kidney biopsy is an important tool to achieve adequate diagnosis of various kidney diseases but also as a gauge for systemic disease. A progressive kidney disease, either in a native kidney or a transplant kidney, will end up with the need for dialysis and/or a new transplantation. To prevent progression various potential drugs are available. However, most diseases are treated with specific protocols of various extents of time. To minimize harmful side effects of medications but also from under-treatment, the diagnosis needs to be as accurate as possible. Therefore, the combination of clinical measures such as antibody titres and kidney biopsy data are necessary. One disadvantage with biopsies is the risk for complications that must be minimized to the greatest possible extent. This thesis aims to increase knowledge about native and transplant kidney biopsy procedures to help minimize the risks for biopsies while at the same time to optimize the diagnostic benefits. Herein data have been available mainly by prospective registration of the procedure and its complications based on a multicentre approach that has been converted into a national registry (Swedish Biopsy Registry, part of the SNR, Svenskt Njurregister, Swedish Renal Registry). The results of the studies within the frame of this thesis together with other references are also summarized as guidelines for biopsies in Table 4 and 5.

The finding in this thesis that women had a greater risk of major biopsy complications in native kidney biopsies than men is still unexplained. Some authors speculate that for the same serum creatinine value women have lower GFRs than men [46]. On the other hand, kidney function was not a risk factor for complications in our studies. Furthermore, patients with lower BMI had a higher risk of major complications after native kidney biopsies. A possible explanation for this can be that the patients with higher BMI are less mobile once placed on the stretcher for biopsy, during the time after the biopsy and that their adipose tissue may compress the kidney capsule and the channel of the injection. But, in patients with high BMI the localization and visualization of the kidneys may be more difficult. In addition, younger patients had more complications after both native and transplant kidney biopsies. This may be explained by the fact that younger patients are more active in the post-biopsy period. In addition to this finding, a study by Harmankaya et al. [80], published after our study, confirmed that elderly patients with a mean age of 71 years (range 65-88 years) had a lower overall complication rate (4%) compared to our study (8.8%) with younger patients (median age 55 years, range 16-90 years).

In the actual interventional ultrasound guidelines of the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) [EFSUMB Guidelines on Interventional Ultrasound (INVUS)] from 2015, our results of female
gender and younger age [77] [Study I] as risk factors for biopsy complications have already been included [81, 82].

We found, in contrast to other studies [45, 47], that high blood pressure was not a risk factor for biopsy complications. These data do not rule out an effect of more extensive hypertension since the patients in our study and in most published studies have at least, in part, control of the blood pressure since previous guidelines recommend aiming at a normotensive condition prior to biopsy, and thereby patients are either on maintenance or temporarily prescribed antihypertensive drugs. We usually performed the biopsies if the blood pressure was less than 160/90 mmHg, otherwise the patients were treated with additional antihypertensive drugs with the aim to achieve a blood pressure below 160/90 mmHg, and thereafter take the biopsies. However, some biopsies were performed when the blood pressure was as high as 197/110 mmHg. Similar data were found in a recent study by Potrezke et al. from 2016 [83]. In a retrospective study of more than 2600 native kidney biopsies, published after our study, they corroborated our findings that high blood pressure was not a risk factor for biopsy complications. In contrast, a retrospective study in 293 native kidney biopsies from 2015 by Kriegshauser et al. [84] found a higher risk for bleeding complications in patients with a blood pressure higher than 140/90 mmHg. In addition, some authors have found an increased risk for bleeding complications in patients with a history of hypertension, irrespective of blood pressure at the time of biopsy [45].

We found that the use of 16 G side-notch needles with 20 mm sample size compared to 18 G, gave better quality and less biopsy complications. There was a higher risk for women having biopsy complications with 18 G side-notch needles than with 16 G. Maybe this finding is related to anatomical or physiological differences between sexes. Another possible explanation can be that a 16 G needle as well as an end-notch needle is firmer than an 18 G side-notch needle, and it is easier to perform biopsies with a firm needle since a more correct localization of the biopsy can be achieved.

The risk for minor complications after native kidney biopsies was higher if the physician had performed less than 30 biopsies during the study period of 8.3 years. Based on these data we recommend that the performer should do at least four biopsies per year. Other authors recommended ten biopsies the first year to achieve competence and thereafter five biopsies per year to maintain competence [37, 85].

IgA-nephritis-patients, not Henoch-Schönlein-nephritis-patients, were shown to have a higher risk for major biopsy complications, especially for severe bleeding. Some authors stated that the coagulation system is impaired in IgA- and Henoch-Schönlein-nephritis [73], although routine coagulation screening tests are normal [86]. Studies in Henoch-Schönlein-nephritis-patients have shown a significant
decrease in fibrin-stabilizing factor (factor XIII) activity [86-89] and that this can result in haemorrhagic complications [87, 89]. Another study showed that the substitution of factor XIII led to a cessation of gastrointestinal bleeding [89] and to an improvement of renal symptoms (both proteinuria and haematuria) [90]. Future studies are needed to clarify if there would be a benefit to measure factor XIII before the biopsy and, if needed, to substitute factor XIII to prevent biopsy complications in IgA-nephritis-patients.

On the other hand a former study by Fisi et al. [91] in 353 patients found that patients with thin glomerular basement membrane disease had a higher risk to develop bleeding complications, and patients with vasculitis, acute interstitial nephritis and rapidly progressive glomerulonephritis had a higher risk for arteriovenous fistulas. However, in that study the native kidney biopsies were performed without real-time ultrasound guidance and with a 14 Gauge biopsy needle [91]. These factors make it difficult to compare the results of this study with our study.

Our study pointed out patients with IgA-nephritis having an increased risk of renal biopsy complications and that amyloidosis was not a risk factor for biopsy complications [79] [Study III]. These findings were later confirmed in a study by Altindal et al. [92]. That study was designed to examine the bleeding risk after native kidney biopsies performed in AA amyloidosis patients. They found no association between biopsy complications and AA amyloidosis but that major bleeding events were more frequent in patients with IgA-nephritis [92].

A study by Mai et al. [12] stated that patients with lupus nephritis stage IV have more major complications after renal biopsies. However, they defined major complications only as bleeding requiring transfusions (0.9%, 8 in 934 biopsies). Since the number of patients in their study was low, a statistical verification was not possible (four of eight (50%) of the complications were in patients with lupus nephritis stage IV). Amyloidosis was reported to be a risk factor for biopsy complications in a former study by Eiro et al. [47]. However, our study [79] [Study III] and other studies [92, 93] could not confirm such risk.

Our correlation analysis showed that the degree of interstitial fibrosis strongly correlated to creatinine and eGFR, while there was a weak correlation between the degree of glomerulosclerosis and kidney function in native kidney biopsies, thus confirming previous studies [94, 95]. In patients with mesangial proliferative glomerulonephritis a relationship has been shown between interstitial damage and GFR and, in addition, that glomerular lesions play a role in the deterioration of renal function [96]. These findings further support the view that glomerulosclerosis and interstitial fibrosis are not solely responsible for loss of kidney function. In our study, the degree of glomerulosclerosis in transplant kidney biopsies, had no
correlation to creatinine and eGFR, but there was a correlation between degree of interstitial fibrosis and creatinine.

Furthermore, a Resistive Index (RI) ≥0.8 was found as a possible predictor for biopsy complications after transplant kidney biopsies. We recommend that these patients should be more closely observed and the biopsies should be performed on an inpatient and not on an outpatient setting, or at least with prolonged observation time after biopsy, to detect and treat biopsy complications in time [Study IV].

We found no correlation between RI and the degree of glomerulosclerosis and interstitial fibrosis in the whole population but more interstitial fibrosis was related to higher RI in the group of RI≥0.8. This is in agreement with a former study [69] and indicates that with a progressive ageing and disease the kidney passes a threshold where the tissue of the kidney gets too firm to withhold bleeding complications. The relation between RI and blood pressure may be difficult to interpret since most patients are on antihypertensive drugs. The poor correlation between kidney function and RI [Study IV] was confirmed by former studies as well [97-99] and indicates that RI is not a helpful variable to estimate kidney function. However, since post-biopsy routines vary widely between centres easy access risk markers such as RI can be helpful to guide the clinician to accept prolonged observation for a patient at risk.

Regarding transplant kidney biopsies, there are a few studies examining risk factors for biopsy complications. Younger age [77, 100] [Study I] can be related to transplant kidney biopsy complications. Besides RI there is little help to indicate a greater risk for complications after transplant kidney biopsies. In our former study [77] [Study I] we found that lower systolic blood pressure, lower MAP and younger age were such risk factors (multivariate analyses showed only younger age). Variables such as needle size, number of biopsy passes, kidney function, diastolic blood pressure, body weight and length, BMI, number and specialty (radiologists and nephrologists) of the performers of the biopsies per center [77] [Study I] predicted no risk for biopsy complications. Thus, the addition of analysis of RI in transplant kidney biopsies appears to be useful as a predictor for biopsy complications and can thus help to improve patients’ safety.

Treatment with immunosuppressive drugs does not influence the RI. This was found in a former study [101] which showed no correlation between the RI and the calcineurin inhibitor-based and calcineurin inhibitor-free treatment.

In the future, an additional diagnostic tool might be the use of urine proteomics. Some authors have stated that the use of urine proteomics can be considered as a “liquid biopsy” since they contain substantial information on the kidney, can be
obtained non-invasively without complications and can be performed by anyone 
multiple times [102]. Furthermore, the urinary peptides can detect chronic kidney 
disease and can be useful for the prognosis of progression [102]. For example, some 
authors found specific urinary biomarkers for IgA-nephritis [103] that can 
distinguish between IgA-nephritis, membranous glomerulonephritis and healthy 
persons [104]. Other authors found specific urinary peptides that can detect diabetic 
nephropathy [105]. We and others believe that it is still not possible to exclude a 
kidney biopsy as an “irreplaceable tool for patient management in nephrology” 
[106]. Although one might consider a kidney biopsy is the “gold standard” for 
morphological diagnosis and classification, for evaluating prognosis and treatment 
in most renal diseases [106], other additive diagnostics help clinicians. Other authors 
state that the urinary peptides consist of metabolized and/or degraded renal proteins 
and these proteins can be influenced by post-renal metabolism and/or degradation, 
whereas the kidney biopsy describe the morphology of the kidney [107]. The kidney 
biopsy is an important tool for diagnosis of renal diseases and patient management 
(treatment and prognosis). Studies showed that the diagnosis changed up to 63% 
[30, 108], and the treatment and prognosis after the results of the kidney biopsy 
changed in more than 40 % of cases depending on the renal diseases [29, 30, 108].

New accurate diagnostic approaches, including specific urinary peptides for IgA- 
nephritis, may reduce the need for biopsies for this diagnose in the future. Until then 
renal biopsy is necessary for adequate diagnostics. In this thesis, we showed that 
patients with IgA-nephritis had a higher risk for biopsy complications. This urges 
for careful follow-up at present stage in patients with suspicion of IgA-nephritis 
(intermittent macroscopic haematuria and proteinuria).

Although urinary proteomics may guide the diagnostics to some extent, still the 
combination of clinical findings such as increase in creatinine, symptoms of gross 
haematuria or proteinuria and hypertension are important to consider. In addition, 
this thesis also points to the importance of optimizing the strategies to minimize the 
risks with native kidney and transplant kidney biopsies for the patient in parallel to 
otimization of diagnostic values. This also includes nursing aspects in preparation, 
performing and surveillance of the biopsy patients. Thereby a conclusive biopsy 
helps to clarify the benefits of specific therapeutic strategies as well as duration of 
treatment of, e.g. cytotoxic and biological drugs. The results from the biopsy help to 
evaluate the risks of therapy as well as the costs that have to be considered besides 
the efficacy of medication (can be evaluated by re-biopsies). Saving a patient from 
progressing into dialysis or transplantation is of great benefit for the patient, as well 
as for their families and society where the patient is active in.

All the results in this thesis implicate that a multidisciplinary collaboration between 
the nephrologists, radiologists, transplant surgeons, urologists, pathologists and 
other professions are important to improve patients` safety and diagnostic quality.
Limitations of this thesis

A limitation of this thesis was the mixed design including prospective and retrospective data. To control the retrospective data, the author of this thesis collected, checked and completed the data after studying the medical charts personally. The same protocol for registration for both retrospective and prospective data was used. Although this study contains data from many biopsies, a statistical limitation is the limited number of biopsy complications when analyzing smaller histological subgroups of diagnoses. As in all studies, there are a number of unknown confounding factors, which can also affect the results. Since our study is a registry study, the quality is dependent on the input of the data. However, in our registry there were very few missing data, the input of data was performed by the author of this thesis and was based on the same specific protocol that was used by all of the participating hospitals. No routine ultrasound examinations were performed routinely after biopsies and some asymptomatic complications can be missed. However, ultrasound examinations after biopsies were done on clinical indications.
Conclusions

Female gender, right-side biopsies in women, younger age and lower BMI are risk factors for major biopsy complications in native kidney biopsies.

Native and transplant kidney biopsies should preferably be performed using 16 G needles. The results are better biopsy quality and less major biopsy complications as compared to 18 G needles. The localization of biopsy within the kidney (native and transplant kidney) does not alter complication rates and biopsy quality. For native kidney biopsies, we recommend that the performer of the biopsy does at least four biopsies per year to reduce the biopsy complication rate.

The risk of major biopsy complications is higher in patients with IgA-nephritis and in patients with a higher degree of glomerulosclerosis in native kidney biopsies. In transplant kidney biopsies, a higher degree of interstitial fibrosis is a risk factor for major complications.

A Resistive Index $\geq 0.8$ is a predictor for major and overall biopsy complications after transplant kidney biopsies. Such findings motivate a more cautious surveillance.
Clinical recommendations

Caution and closer observation after native kidney biopsies are recommended in women, in biopsies from their right kidney, in younger patients, patients with lower BMI and patients with suspicion of having IgA-nephritis.

Native and transplant kidney biopsies should be performed with 16 Gauge biopsy needles.

Native kidney biopsies should be performed by physicians who do at least four biopsies per year.

Increased surveillance is motivated after transplant kidney biopsies with a Resistive Index ≥0.8 in the kidney transplant.

Within the frame of the studies in this thesis and the references given, the following guidelines for renal biopsies to minimize risk and optimize biopsies can be given in Table 4 and 5.
### Recommendations for native kidney biopsy

<table>
<thead>
<tr>
<th>Variables</th>
<th>Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Younger (&lt;47 years) more caution</td>
</tr>
<tr>
<td>Female gender</td>
<td>Prefer left kidney</td>
</tr>
<tr>
<td>Male gender</td>
<td>No preference of kidney site</td>
</tr>
<tr>
<td>BMI</td>
<td>&lt;26 more cautious</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>Withdrawn 7 days before biopsy</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Withdrawn 7 days before biopsy</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Withdrawn 7 days before biopsy</td>
</tr>
<tr>
<td>NSAID</td>
<td>Withdrawn 3 days before biopsy</td>
</tr>
<tr>
<td>Blood pressure, systolic</td>
<td>Maximum 160 mmHg</td>
</tr>
<tr>
<td>Blood pressure, diastolic</td>
<td>Maximum 90 mmHg</td>
</tr>
<tr>
<td>Mean arterial pressure (MAP)</td>
<td>No specific data</td>
</tr>
<tr>
<td>Desmopressin prophylaxis</td>
<td>May be protective</td>
</tr>
<tr>
<td>Resistive Index</td>
<td>Recommendations missing</td>
</tr>
<tr>
<td>Physicians</td>
<td>Recommend at least 4 biopsies/year</td>
</tr>
<tr>
<td>Needle size</td>
<td>Prefer 16 Gauge 20 mm (side-notch)</td>
</tr>
<tr>
<td>Biopsy location in kidney</td>
<td>Prefer tangential biopsy, no specific location</td>
</tr>
<tr>
<td>Specific diagnosis anticipated</td>
<td>IgA nephritis- more caution</td>
</tr>
</tbody>
</table>
Table 5. Guidelines for transplant kidney biopsies.

<table>
<thead>
<tr>
<th>Recommendations for transplant kidney biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variables</strong></td>
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<tr>
<td>Age</td>
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<tr>
<td>Resistive Index</td>
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<tr>
<td>Physicians</td>
</tr>
<tr>
<td>Needle size</td>
</tr>
<tr>
<td>Biopsy location in kidney</td>
</tr>
<tr>
<td>Specific diagnosis anticipated</td>
</tr>
</tbody>
</table>
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