Studies in Patients with Kidney Diseases

Principal Investigator: Florian Kronenberg

Background:

Patients with chronic kidney disease have one of the highest risks known for atherosclerotic complications. They have furthermore pronounced disturbances in lipoprotein metabolism. The interconnection between these disturbances and atherosclerotic complications in this patient group is not well understood and paradox in several ways. The following topics related to cardiovascular disease and progression of kidney disease are a focus of our research:

Lipoprotein(a) and the Kidney

Lp(a) and apo(a) size polymorphism in chronic kidney disease: We investigated Lp(a) concentrations and the apo(a) size polymorphism in several patient groups with various stages of impairment of renal function and with various treatment modalities **[1]**. Lp(a) starts to increase in the earliest stages of renal disease often long before glomerular filtration rate is decreased **[2]**. However, this holds true only for patients with high molecular weight (HMW) apo(a) isoforms and not those with low molecular weight (LMW) apo(a) isoforms when compared to apo(a) isoform-matched controls. This apo(a) isoform-specific increase can be observed in non-nephrotic renal disease and hemodialysis patients but not in patients treated by continuous ambulatory peritoneal dialysis (CAPD) or in patients with nephrotic syndrome **[3-7]**. In accordance, a decrease of Lp(a) following a successful kidney transplantation can be observed in hemodialysis patients with large apo(a) isoforms **[4,6]** (Figure 1).

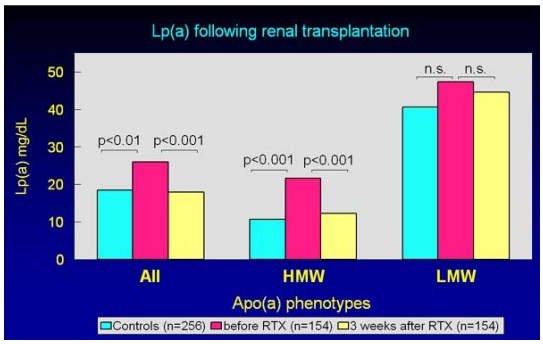

Figure 1: *Mean plasma Lp(a) concentrations in 256 controls and 154 hemodialysis patients with end-stage renal disease before and after renal transplantation. Lp(a) levels were also calculated separately for individuals with low (LMW) and high-molecular weight (HMW) apo(a) phenotypes. Three weeks after renal transplantation the Lp(a) levels had decreased to values observed in a control group. These data confirm the apo(a) isoform-specific elevation of Lp(a) in hemodialysis patients and clearly demonstrate that the elevation of Lp(a) in these patients is nongenetic and obviously caused by the disease. Data according to references [3-5].*

Lp(a), apo(a) size polymorphism and atherosclerosis in CKD: We published for the first time an association of the apo(a) size polymorphism and the extent of carotid atherosclerosis in hemodialysis patients **[8]**. These cross-sectional investigations were extended to coronary artery disease **[9,10]**. In a five-year prospective study in 440 hemodialysis patients, the apo(a) size polymorphism was identified as an excellent predictor for coronary events **[10]** (Figures 2). This was the first prospective study showing the importance of the apo(a) polymorphism in this high-risk atherosclerosis group. In the meanwhile several other studies have confirmed this association (for review, see reference **[11]**). Furthermore, we demonstrated in the prospective population-based Bruneck Study that depending on the apo(a) size polymorphism the same amount of Lp(a) concentrations is associated with a different risk for advanced carotid atherosclerosis **[12]**.

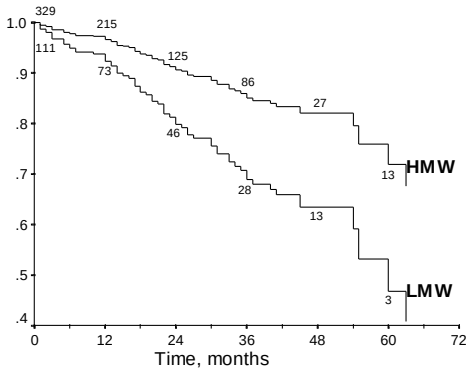

Figure 2*: Coronary event-free survival in hemodialysis patients with high (HMW) and low molecular weight (LMW) apo(a) phenotypes. Adjusted results are obtained from a multiple Cox proportional hazards regression analysis [10].*

Role of the kidney for turnover of lipids: A vicious cycle has been suggested in uremia in which the decreased catabolism of atherogenic lipoproteins such as LDL, IDL and Lp(a) leads to their increased plasma residence time and further modification of these lipoproteins by oxidation, carbamylation and glycation. Using stable isotope techniques, we showed that the plasma residence time of these particles is more than twice as long in hemodialysis patients as in non-uremic subjects. This reduced catabolism, however, is masked by the decreased production of LDL, resulting in near-normal plasma levels of LDL **[13]**. The production rate of Lp(a) in hemodialysis patients is similar as in controls which together with the doubled residence time results in elevated Lp(a) levels **[14]**. This is in line with our earlier detection of arteriovenous renovascular differences for Lp(a) which demonstrated that the kidney is able to extract large amounts of Lp(a) from the systemic circulation. This is a clear indication that the kidney is involved in the metabolism of Lp(a) **[15]**.

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Apolipoprotein A-IV and the Kidney

In patients with renal disease we observed that apoA-IV concentrations start to increase during the earliest phases of renal impairment which makes apoA-IV an early marker of renal impairment **[16]**. Dialysis patients have twice as high plasma concentrations than healthy controls **[17,18]**. In the "Mild to Moderate Kidney Disease Study" (MMKD) we found that the presence of high concentrations of apoA-IV is a reliable predictor for a progression of kidney disease during the following years of observation. This association was independent from the baseline glomerular filtration rate **[19]**. For more information on ApoA-IV, see project "Apolipoprotein A-IV in Health and Disease".

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Mild to Moderate Kidney Disease Study (MMKD)

The "Mild to Moderate Kidney Disease" (MMKD) Study was established in the mid nineties and aims to investigate possible risk factors or risk markers for the progression of CKD. More than half of the recently identified risk markers for the progression of CKD were the first time described in the MMKD Study **[20]**. For detailed information, see MMKD Study.

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INVOR Study (Study of Incident Dialysis Patients in Vorarlberg)

The INVOR-Study is a single-center, prospective, observational cohort study of incident hemodialysis and peritoneal dialysis patients in Vorarlberg, the westernmost province of Austria counting approximately 400,000 inhabitants. All incident dialysis patients starting chronic dialysis treatment between May 1st, 2000 and April 30th, 2006 were enrolled. This inception cohort was established by Ulrich Neyer (former Head of Nephrology and Dialysis of the Feldkirch Hospital) and is still strongly supported by him and his successor Karl Lhotta. Our group is responsible for data management, data cleaning and statistical analysis. The manuscripts are written in cooperation.

A total of 235 patients were included in the study and these patients are prospectively followed until today. Although the sample size is relatively low, the study has a major strength: we use in our analysis the entire data collected through the whole observation period. That means we do not only consider a baseline concentration of a certain measured parameter but the concentrations as well as all other covariates recorded during the entire observation period. For frequently measured parameters such as hemoglobin up to more than 200 measurements are

used in the data analysis using a time-dependent Cox regression model. This results in a depth of data never used before in dialysis patients over such a long observation period.

The use of a time-dependent modeling has several advantages since it does not consider only one or a few data points but the full spectrum of data in each patient that occurred during follow-up. Studies which include only a baseline value or values of the first few months consider usually the most instable phase of treatment when a patient starts dialysis treatment. This vulnerable phase is associated with a very high mortality and does not necessarily reflect the more stable latter phases of treatment with often much better laboratory values. The first paper on that cohort was published recently **[21]**.

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The Family Heart and Kidney Study (FHKS)

The "Family Heart and Kidney Study" is an ongoing prospective multicenter cohort study that started in 2004 with the recruitment of the first patients. It aims to investigate the genetic variability of selected candidate genes influencing lipoprotein metabolism as well as their influence on atherosclerotic complications in the high-risk group of hemodialysis patients. Patients aged from 25 to 75 years being on dialysis treatment since at least four weeks but no longer than three years are being included in the study independently of the underlying kidney disease. Exclusion criteria are former organ transplantations and malignancy.

Blood samples are taken after an overnight fast following the long dialysis time interval. We implemented a questionnaire survey to collect data to prevalent cardiovascular diseases and their risk factors, family history of cardiovascular disease as well as quality of live of the dialysis patients.

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German Chronic Kidney Disease Study (GCKD)

The GCKD Study aims to establish a comprehensive national cohort study in patients with moderate kidney impairment (eGFR 30-60 ml/min) under care of nephrologists. We aim to investigate etiology, modifying factors and consequences of progressive chronic kidney disease.

Our main hypothesis is that new technologies such as genomics, proteomics, metabolomics will allow to identify yet unknown risk factors or markers for a progression of kidney diseases and the development of cardiovascular events related to chronic kidney disease. Based on the findings new diagnostic and therapeutic targets should be elucidated. The "Mild to Moderate Kidney Disease Study" (MMKD) can be considered as a pilot or feasibility study for the GCKD Study.

During 2007/08 the following nine partners applied for funding of this cohort study at the "Federal Ministry of Education and Research" (BMBF) and the "KFH Stiftung für Präventivmedizin" to establish GCKD.

- Kai-Uwe Eckardt, University of Erlangen-Nuremberg (coordinator)
- Jürgen Floege, RWTH Aachen
- Olaf Gefeller, University of Erlangen-Nuremberg
- Hermann Haller, Hannover Medical School
- Florian Kronenberg, Innsbruck Medical University
- Peter Oefner, University of Regensburg
- Andre Reis, University Clinic Erlangen
- Christoph Wanner, University Clinic Würzburg
- Gunter Wolf, University of Jena

For more details on the study, see: www.gckd.de

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ARO CKD Research Initiative

The **A**nalyzing data, **R**ecognizing excellence, **O**ptimizing outcomes (ARO) CKD research initiative aims to identify risk factors and opportunities for intervention in a large European dialysis cohort using a common database of patients from more than 150 Fresenius Medical Care dialysis centers in Eastern and Western Europe (EU-FME). The baseline study description **[22]** and first results are described elsewhere **[23,24]**.

Steering Committee:

Co-chairs:

- Kai-Uwe Eckardt, University of Erlangen-Nuremberg, Erlangen, Germany
- Jürgen Floege, RWTH University of Aachen, Aachen, Germany

Members:

- Pedro Aljama, Hospital Reina Sofia de Cordoba, Cordoba, Spain
- Stefan D Anker, Charité, Campus Virchow-Klinikum, Berlin, Germany
- Bernard Canaud, Hôpital Lapeyronie, Montpellier, France
- Angel LM de Francisco, Hospital Universitario Valdecilla, Santander, Spain
- Tilman B. Drüeke, Hôpital Necker, Université Paris 5, Paris, France
- Florian Kronenberg, Innsbruck Medical University, Innsbruck, Austria
- Iain C Macdougall, King's College Hospital, London, UK

- Guntram Schernthaner, Rudolfstiftung Hospital, Vienna, Austria
- Peter Stenvinkel, Karolinska Institute, Stockholm, Sweden
- David C Wheeler, University College London Medical School, London, UK

Fresenius Medical Care:

- Charles Chazot, Centre de Rein Artificiel, Tassin la Demi-Lune, France
- Daniele Marcelli, Fresenius Medical Care, Bad Homburg, Germany
- Jutta Passlick-Deetjen, Fresenius Medical Care, Bad Homburg, Germany

Amgen:

- Vasily Belozeroff, Amgen Inc., Thousand Oaks, California, USA
- Bruno Fouqueray, Amgen (Europe) GmbH, Zug, Switzerland
- Joseph Kim, Amgen Ltd, Uxbridge, United Kingdom
- Bart Molemans, Amgen Ltd, Uxbridge, United Kingdom

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Team Members and Partners of Our Studies

Team members of the Division of Genetic Epidemiology (current and former):

Barbara Kollerits, Gisela Sturm, Claudia Lamina, Eva Boes, Evi Trenkwalder, Benjamin Ezeh, Michael Frischmann, Hans Dieplinger

All of our projects would not have been possible without the continuous support of the following clinical partners which we very much appreciate.

Main partners of the MMKD Study Group:

The following persons were/are members of the "Mild and Moderate Kidney Disease" (MMKD) Study Group: Erich Kuen, Division of Genetic Epidemiology, Innsbruck Medical University (Innsbruck, Austria); Paul König, Innsbruck University Hospital (Innsbruck, Austria); Günter Kraatz, Ernst Moritz Arndt University (Greifswald, Germany); Johannes F.E. Mann, München Schwabing Hospital (Munich, Germany); Gerhard A. Müller, Georg August University (Göttingen, Germany); Ulrich Neyer, Feldkirch Hospital (Feldkirch, Austria); Danilo Fliser and Hans Köhler, Medizinische Universitätskliniken des Saarlandes (Homburg/Saar, Germany); Peter Riegler, Bozen Hospital (Bozen, Italy).

Main partners of the INVOR Study Group:

Ulrich Neyer, Karl Lhotta, Emanuel Zitt, Florian Knoll, Otto Freistätter; Feldkirch Hospital, Austria.

Main partners of the FHKS Study Group:

We appreciate the collaboration with the following members of the "Family Heart and Kidney Study" (FHKS) Group: Paul König (Innsbruck University Hospital, Innsbruck, Austria); Michael Koch and Iva Poludniak (Nephrologisches Zentrum Mettmann, Germany); Ulrich Neyer, Susanne Linder, Christine Stüttler-Gut, Kathrin Berchtold, Hannelore Sprenger-Mähr, Sabina Smodek, Lisa Schuler, (Feldkirch Hospital, Feldkirch, Austria); Martin Auinger (Krankenhaus Hietzing, Vienna, Austria); Martin Wiesholzer (St. Pölten Hospital, Austria); Nikolaus Zambelis and Wilfried V. Jilly (Pörtschach am Wörther See and Klagenfurt, Austria); Josef Kovarik, Ursula Lang and Heinz Fuhrmann (Wilhelminenspital Vienna, Austria); Ludwig Knabl (Zams Hospital, Austria).

Main partners of other studies in patients with kidney diseases:

- Paul König, Karl Lhotta, Gert Mayer (Department of Clinical Nephrology)
- Claudia Bösmüller, Dietmar Öfner, Alfred Königsrainer, Raimund Margreiter (Department of Transplant Surgery)
- Wolfgang Sturm, Hermann Kathrein (Department of Internal Medicine)
- Ulrich Neyer, Ernst Gröchenig, Michael Mündle, Michael Längle (Feldkirch Hospital)
- Martin Auinger, Karl Irsigler, Rudolf Prager (Lainz Hospital, Vienna)
- Martin Wiesholzer, Andreas Pribasnig (St. Pölten Hospital)
- Thomas Meisl, Ursula Lang (Wilhelminenspital Vienna)
- Dietmar Geissler, Georg Pinter (Klagenfurt Hospital)
- Reinhard Kramar (Wels Hospital)
- Michael Koch, Bernd Grabensee (University of Düsseldorf, D)

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Selected Publications

1. Kronenberg F, Utermann G, Dieplinger H: Lipoprotein(a) in renal disease. ***American Journal of Kidney Diseases*** 27: 1-25, 1996. *[PubMed]*
2. Kronenberg F, Kuen E, Ritz E, Junker R, König P, Kraatz G, Lhotta K, Mann JFE, Müller GA, Neyer U, Riegel W, Riegler P, Schwenger V, Von Eckardstein A: Lipoprotein(a) serum concentrations and apolipoprotein(a) phenotypes in mild and moderate renal failure. ***Journal of the American Society of Nephrology*** 11: 105-115, 2000. *[PubMed]*
3. Dieplinger H, Lackner C, Kronenberg F, Sandholzer C, Lhotta K, Hoppichler F, Graf H, König P: Elevated plasma concentrations of lipoprotein(a) in patients with end-stage renal disease are not related to the size polymorphism of apolipoprotein(a). ***Journal of Clinical Investigation*** 91: 397-401, 1993. *[PubMed]*
4. Kronenberg F, König P, Lhotta K, Öfner D, Sandholzer C, Margreiter R, Dosch E, Utermann G, Dieplinger H: Apolipoprotein(a) phenotype-associated decrease in lipoprotein(a) plasma concentrations after renal transplantation. ***Arteriosclerosis and Thrombosis*** 14: 1399-1404, 1994. *[PubMed]*
5. Kronenberg F, König P, Neyer U, Auinger M, Pribasnig A, Lang U, Reitinger J, Pinter G, Utermann G, Dieplinger H: Multicenter study of lipoprotein(a) and apolipoprotein(a) phenotypes in patients with end-stage renal disease treated by hemodialysis or continuous

ambulatory peritoneal dialysis. ***Journal of the American Society of Nephrology*** 6: 110-120, 1995. [PubMed]

6. Kronenberg F, Lhotta K, König P, Margreiter R, Dieplinger H, Utermann G: Apolipoprotein(a) isoform-specific changes of lipoprotein(a) after kidney transplantation. ***European Journal of Human Genetics*** 11: 693-699, 2003. [PubMed]
7. Kronenberg F, Lingenhel A, Lhotta K, Rantner B, Kronenberg MF, König P, Thiery J, Koch M, Von Eckardstein A, Dieplinger H: The apolipoprotein(a) size polymorphism is associated with nephrotic syndrome. ***Kidney International*** 65:606-612, 2004. [Pub-Med]
8. Kronenberg F, Kathrein H, König P, Neyer U, Sturm W, Lhotta K, Gröchenig E, Utermann G, Dieplinger H: Apolipoprotein(a) phenotypes predict the risk for carotid atherosclerosis in patients with end-stage renal disease. ***Arteriosclerosis and Thrombosis*** 14: 1405-1411, 1994. [PubMed]
9. Koch M, Kutkuhn B, Trenkwalder E, Bach D, Grabensee B, Dieplinger H, Kronenberg F: Apolipoprotein B, fibrinogen, HDL cholesterol and apolipoprotein(a) phenotypes predict coronary artery disease in hemodialysis patients. ***Journal of the American Society of Nephrology*** 8: 1889-1898, 1997. [PubMed]
10. Kronenberg F, Neyer U, Lhotta K, Trenkwalder E, Auinger M, Pribasnig A, Meisl T, König P, Dieplinger H: The low molecular weight apo(a) phenotype is an independent predictor for coronary artery disease in hemodialysis patients: a prospective follow-up. ***Journal of the American Society of Nephrology*** 10: 1027-1036, 1999. [PubMed]
11. Kwan BCH, Kronenberg F, Beddhu S, Cheung AK: Lipoprotein metabolism and lipid management in chronic kidney disease. ***Journal of the American Society of Nephrology*** 18:1246-1261, 2007 (invited review). [Pub-Med]
12. Kronenberg F, Kronenberg MF, Kiechl S, Trenkwalder E, Santer P, Oberhollenzer F, Egger G, Utermann G, Willeit J: Role of lipoprotein(a) and apolipoprotein(a) phenotype in atherogenesis: prospective results from the Bruneck Study. ***Circulation*** 100: 1154-1160, 1999. [PubMed]
13. Ikewaki K, Schaefer JR, Frischmann ME, Okubo K, Hosoya T, Mochizuki S, Dieplinger B, Trenkwalder E, Schweer H, Kronenberg F, Koenig P, Dieplinger H: Delayed in vivo catabolism of Intermediate-Density Lipoprotein and Low-Density Lipoprotein in hemodialysis patients as potential cause of premature atherosclerosis. ***Arteriosclerosis, Thrombosis and Vascular Biology*** 25:2615-2622, 2005. [Pub-Med]
14. Frischmann ME, Kronenberg F, Trenkwalder E, Schaefer J, Schweer H, Dieplinger B, König P, Ikewaki K, Dieplinger H: In vivo turnover study demonstrates diminished clearance of lipoprotein(a) in hemodialysis patients. ***Kidney International*** 71:1036-1043, 2007. [Pub-Med]
15. Kronenberg F, Trenkwalder E, Lingenhel A, Friedrich G, Lhotta K, Schober M, Moes N, König P, Utermann G, Dieplinger H: Renovascular arteriovenous differences in Lp(a) plasma concentrations suggest removal of Lp(a) from the renal circulation. ***Journal of Lipid Research*** 38: 1755-1763, 1997. [PubMed]
16. Boes E, Fliser D, Ritz E, König P, Lhotta K, Mann JFE, Müller GA, Neyer U, Riegel W, Riegler P, Kronenberg F, for the MMKD Study Group: Apolipoprotein A-IV predicts progression of chronic kidney disease: The Mild to Moderate Kidney Disease (MMKD) Study. ***Journal of the American Society of Nephrology*** 17:528-536, 2006. [Pub-Med]
17. Kronenberg F, König P, Neyer U, Auinger M, Pribasnig A, Lang U, Reitinger J, Pinter G, Utermann G, Dieplinger H: Multicenter study of lipoprotein(a) and apolipoprotein(a) phenotypes in patients with end-stage renal disease treated by hemodialysis or continuous ambulatory peritoneal dialysis. ***Journal of the American Society of Nephrology*** 6: 110-120, 1995. [PubMed]

18. Kronenberg F, Lingenhel A, Neyer U, Lhotta K, König P, Auinger M, Wiesholzer M, Andersson H, Dieplinger H: Prevalence of dyslipidemic risk factors in hemodialysis and CAPD patients. ***Kidney International*** 63, Suppl. 84: S113-S114, 2003. [PubMed]

19. Kronenberg F, Kuen E, Ritz E, Junker R, König P, Kraatz G, Lhotta K, Mann JFE, Müller GA, Neyer U, Riegel W, Riegler P, Schwenger V, Von Eckardstein A: Apolipoprotein A-IV serum concentrations are elevated in mild and moderate renal failure. ***Journal of the American Society of Nephrology*** 13: 461-469, 2002. [PubMed]

20. Kronenberg F: Emerging risk factors and markers of chronic kidney disease progression. ***Nature Reviews Nephrology*** 5:677-689, 2009. [Pub-Med]

21. Sturm G, Lamina C, Zitt E, Lhotta K, Lins F, Freistätter O, Neyer U, Kronenberg F: Sex-specific association of time-varying hemoglobin values with mortality in incident dialysis patients. ***Nephrolology, Dialysis, Transplantation*** 25:2715-2722, 2010. [PDF]

22. De Francisco ALM, Kim J, Anker SD, Belozeroff V, Canaud B, Chazot C, Drüeke TB, Eckardt KU, Floege J, Kronenberg F, Macdougall IC, Marcelli D, Molemans B, Passlick-Deetjen J, Schernthaner G, Stenvinkel P, Wheeler DC, Fouqueray B, Aljama P: An epidemiological study of hemodialysis patients based on the European Fresenius Medical Care Hemodialysis Network: Results of the ARO Study. ***Nephron Clinical Practice*** 118:c143-c154, 2011. [Pub-Med]

23. Eckardt KU, Kim J, Kronenberg F, Aljama P, Anker SD, Canaud B, Molemans B, Stenvinkel P, Schernthaner G, Ireland E, Fouqueray B, Macdougall IC: Hemoglobin variability does not predict mortality in European hemodialysis patients. ***Journal of the American Society of Nephrology*** 21:1765-75. [Pub-Med]

24. Floege J, Kim J, Ireland E, Chazot C, Drueke T, de Francisco A, Kronenberg F, Marcelli D, Passlick-Deetjen J, Schernthaner G, Fouqueray B, Wheeler DC, on behalf of the ARO Investigators: Serum iPTH, calcium and phosphate and the risk of mortality in a European hemodialysis population. ***Nephrolology, Dialysis, Transplantation*** (in press). [Pub-Med]