Anticoagulants in kidney disease

Frida Welander

UMEÅ UNIVERSITET

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Frida Welander

Department of Public Health and Clinical Medicine
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To my children,
Kerstin, Gösta and Märta

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Abstract

Background

Patients with chronic kidney disease (CKD) and atrial fibrillation (AF) are at high risk of ischemic stroke. Evidence is lacking if patients with advanced CKD or on dialysis benefit from oral anticoagulants (OAC) as stroke prophylaxis. There is also no clear evidence on the safety and efficacy of prophylactic anticoagulants (PAC) in the prothrombotic state nephrotic syndrome (NS).

Aims

To investigate effectiveness and risks of oral anticoagulants as stroke prophylaxis in chronic kidney disease with atrial fibrillation.

To examine the role of warfarin treatment quality as a predictor for ischemic stroke and bleeding in CKD.

To investigate benefits and risks with prophylactic anticoagulants in patients with nephrotic syndrome and elucidate risk factors for thrombosis and bleeding.

Methods

A cohort of patients with non-valvular atrial fibrillation (NVAF) and CKD GFR category 3–5 (G3–G5) or on dialysis (G5D) was created by combining data from national health care- and quality registries between 2009-2018. Included registries were the Swedish Renal Registry, AuriculA, The Stroke Register and The Swedish National Patient Register. G3 was defined as GFR 30-59ml/min/1.73m^2, G4: 15-29, G5: <15, G5D: on dialysis. **Paper I** compared patient time on warfarin with patient time on no OAC treatment using Cox regression. **Paper II** compared DOAC and warfarin using the same methods. **Paper III** investigated the effect of increasing warfarin treatment quality, measured as individual time in therapeutic range (iTTR). Primary outcomes in paper I-III were ischemic stroke and major bleeding. **Paper IV**, a retrospective medical records study included adults with NS between 2010-2019 in the county of Västernorrland, Sweden. Outcomes were venous thromboembolism (VTE), bleeding and death. Patients divided into PAC- and no PAC group were compared using Fisher's exact test. Patient time was divided into serum/plasma (S/P)-albumin intervals and VTE- and bleeding rates were calculated.

Results

Paper I: At study start 12106 patients were included, 21.4% had G3, 43.5% G4, 11.6% G5 and 23.6% G5D. Warfarin, TTR 70%, compared to no treatment conferred lower risk for ischemic stroke in all patients,

hazard ratio 0.51 (95% confidence interval 0.41-0.64). Warfarin was associated with higher risk of bleeding, 1.28 (1.14-1.43) in G3-G5D. Major bleedings were more than twice as common as ischemic stroke in G5-5D, irrespective of warfarin or no OAC treatment. Death was more than halved on warfarin compared to no treatment in all patients, 0.46 (0.42-0.50).

Paper II: For comparing DOAC and warfarin, 2453 patients were included. DOAC compared to warfarin, TTR 67%, was associated with lower hazard of major bleeding, HR 0.71 (95%CI 0.53-0.96) but no difference in the risk of ischemic stroke. Mortality was higher during DOAC treatment, 1.24 (1.01-1.53), presumably not a causal association since less fatal bleedings on DOAC occurred.

Paper III: Of 2379 patients on warfarin 21.9% had G3, 47.5% G4, 10.8% G5 and 19.8% G5D. TTR in G3 was 75.6%, G4 72.2%, G5 67.6% and G5D 62.0%. Increase by 10 percentage points iTTR conferred lower risk of major bleeding, ischemic stroke and death for all patients, HR 0.91 (95%CI 0.87-0.94), 0.92 (0.85-0.99) and 0.88 (0.85-0.90).

Paper IV: Of 95 included patients with NS, 40 patients had PAC and 55 patients had no PAC. Seven VTE (7.4%) and 17 bleedings (18%) were found, 4 patients (4.2%) experienced major bleedings. Outcomes didn't differ significantly between the PAC and no PAC group. Time with S/P-albumin <20g/L conferred higher rates/100 years of VTE with incidence rate ratio, IRR, 21.7 (95%CI 4.5–116.5) and bleeding, IRR 5.0 (1.4 –14.7), compared to time with S/P-albumin≥20g/L.

Conclusions

High quality warfarin treatment compared to no OAC is associated with lower risk of ischemic stroke but higher risk of bleeding in patients with NVAF and CKD G3-G5D. Improved warfarin treatment quality seems beneficial regarding the risk of both bleeding and ischemic stroke. DOAC treatment is associated with lower risk of bleeding compared to warfarin in G3-G5D. The rate of major bleeding exceeds the rate of ischemic stroke in both OAC-treated and untreated patients. The risk of bleeding is particularly high in G5-5D and therefore, anticoagulants should not be prescribed by routine in these patients with AF. Larger randomised controlled trials (RCTs) need to confirm the possible benefit of DOAC compared to warfarin and establish whether anticoagulants are warranted in patients with NVAF and advanced CKD or on dialysis. Awaiting RCTs it might be reasonable to use OAC in selected patients on dialysis, with low risk of bleeding and high risk of ischemic stroke. If choosing warfarin, close monitoring is recommended. DOAC seems to be an appealing alternative to warfarin. Patients with NS have high risk of both VTE and bleeding, especially during time with S/P-albumin<20g/L. RCTs could elucidate whether PAC is warranted in NS.

Abbreviations

ADP	Adenosine diphosphate
AF	Atrial fibrillation
APC	Activated protein c
ARN	Anticoagulant-related nephropathy
ATE	Arterial thromboembolism
AUC	Area under curve
B	Blood
BCG	Bromocresol green
BCP	Bromocresol purple
BID	Bidaily
BMI	Body mass index
CG	Cockcroft gault
CI	Confidence interval
CIF	Cumulative incidence function
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
DOAC	Direct oral anticoagulants
DVT	Deep venous thrombosis
eGFR	Estimated GFR
$eGFR_{Cr}$	Estimated GFR by creatinine
$eGFR_{Cy}$	Estimated GFR by cystatin C
EMA	European medicines agency
FDA	The United States food and drug administration
FSGS	Focal segmental glomerulosclerosis
FV	Factor V
G3	GFR category 3
G5D	GFR category 5 on dialysis
GFR	Glomerular filtration rate
GI	Gastrointestinal
HD	Hemodialysis
HR	Hazard ratio
ICD	International classification of diseases
INR	International normalized ratio
IRR	Incidence rate ratio
iTTR	Individual time in therapeutic range
IU	International units
KM	Kaplan-Meier
KRT	Kidney replacement therapy
LAAC	Left atrial appendage closure
LMWH	Low molecular weight heparin
MBD	Mineral and bone disorder
MCD	Minimal change disease
MGP	Matrix gla protein
MN	Membranous nephropathy
MPGN	Membranoproliferative glomerulonephritis
NPR	The Swedish national patient register
NS	Nephrotic syndrome
NVAF	Non-valvular atrial fibrillation
OAC	Oral anticoagulants
OD	Once daily
PAC	Prophylactic anticoagulants
PCI	Percutaneous coronary intervention
PD	Peritoneal dialysis
PDR	The Swedish prescribed drug register
PE	Pulmonary embolism
Q	Quartile
RAAS	Renin-angiotensin-aldosterone system
RCT	Randomised controlled trial
RVT	Renal vein thrombosis
S/P	Serum/Plasma
SCr	Serum creatinine
SGLT-2	Sodium-glucose cotransporter-2
SR	The Swedish stroke register
SRR	Swedish renal registry
TF	Tissue factor
TFPI	Tissue factor pathway inhibitor
TIA	Transient ischemic attack
tPA	Tissue plasminogen activator
TTR	Time in therapeutic range
U	Urine
U-alb/ U-crea	Urine-albumin/Urine-creatinine
UFH	Unfractionated heparin
uPA	Urokinase-type plasminogen activator
VKA	Vitamin-K antagonist
VTE	Venous thromboembolism
vWF	Von Willebrand factor
WRN	Warfarin-related nephropathy

List of original papers

This thesis is based on the papers as follows, which will be referred to by their Roman numerals.

I. Welander F, Renlund H, Dimény E, Holmberg H, Själander A. Efficacy and safety of warfarin in patients with non-valvular atrial fibrillation and CKD G3-G5D. Clinical Kidney Journal. 2022 Jan 28;15(6):1169-1178. Erratum in: Clinical Kidney Journal. 2023 Mar 21;16(6):1043.

II. Welander F, Renlund H, Dimény E, Holmberg H, Själander A. Direct oral anticoagulants versus warfarin in patients with non-valvular atrial fibrillation and CKD G3-G5D. Clinical Kidney Journal. 2023 Jan 5;16(5):835-844.

III. Welander F, Renlund H, Dimény E, Holmberg H, Själander A. Warfarin treatment quality and outcomes in patients with non-valvular atrial fibrillation and CKD G3-G5D. Thrombosis Research. 2023 Sep;229:131-138.

IV. Welander F, Holmberg H, Dimény E, Jansson U, Själander A. Prophylactic anticoagulants to prevent venous thromboembolism in patients with nephrotic syndrome-A retrospective observational study. PLoS One. 2021 Jul 28;16(7):e0255009.

Enkel sammanfattning på svenska

Bakgrund:

Kronisk njursjukdom, CKD, definieras som ihållande nedsatt njurfunktion, mätt som nedsatt filtrationshastighet i njurens små kärlnystan eller andra tecken på njurskada, såsom äggviteläckage i urinen. CKD kan orsakas av flera olika sjukdomar som till exempel diabetes, högt blodtryck eller inflammation i de små kärlnystanen (glomerulonefrit). CKD delas in i stadier där stadium 3 innebär moderat nedsatt njurfunktion, stadium 4 är allvarligt nedsatt njurfunktion och stadie 5 innebär att patienten så småningom behöver njurtransplanteras eller starta dialys (stadium 5D). CKD drabbar upp till 10% av befolkningen och bidrar till ökad risk för en rad följdsjukdomar inklusive hjärtrytmrubbningen förmaksflimmer. Av patienter med CKD stadium 4–5 har upp till 20-25% förmaksflimmer. När hjärtats förmak flimrar står blodet mer still och får chans att levra sig, bilda blodproppar. Detta kan leda till att små proppar lossnar, far i väg från hjärtat till hjärnan och orsakar stroke. Patienter med förmaksflimmer i den allmänna befolkningen behandlas ofta med blodförtunnande läkemedel, antikoagulantia, för att förhindra stroke. Traditionellt sett har man använt den blodförtunnande medlet warfarin. Det senaste decenniet har nya blodförtunnande läkemedel, DOAK, börjat dominera. Patienter med mer än moderat nedsatt njurfunktion har till största del uteslutits från stora randomiserade läkemedelsprövningar (RCTs) av antikoagulantia. Detta beror delvis på att CKD i sig medför ökad blödningsrisk. Därför är det oklart om patienter med allvarligt nedsatt njurfunktion och förmaksflimmer ska ha blodförtunnande, eller om den ökade blödningsrisken medför att antikoagulantia ska undvikas.

Nefrotiskt syndrom är ett specialfall av njursjukdom som innebär ökad risk för venösa proppar. Traditionellt sett har dessa patienter behandlats med förebyggande blodförtunning, men det saknas studier på dess effekt och säkerhet.

Syftet med våra studier var att undersöka nytta och risk med blodförtunning hos patienter med njursvikt stadium 3-5D samt hos patienter med nefrotiskt syndrom.

Metod:

Drygt 12 000 patienter med förmaksflimmer och CKD stadium 3-5D har identifierats med hjälp av samkörning av Svenskt Njurregister och

Patientregistret. Blodförtunnande behandling identifieras med AuriculA, register för förmaksflimmer och antikoagulantia, samt Läkemedelsregistret. Jämförelse mellan grupperna görs med regressionsanalyser justerade för kända riskfaktorer för stroke och blödning, så som ålder, tidigare stroke och njurfunktion. I **studie I** jämförs warfarin och ingen blodförtunning med avseende på risken för stroke pga. propp samt allvarlig blödning. I **studie II** jämförs warfarin och DOAK med avseende på samma utfall. I **studie III** studeras hur kvaliteten av warfarinbehandlingen spelar roll för utfallen. **Studie IV** identifierar patienter med nefrotiskt syndrom i Västernorrland via journalgranskning. Patienter som fått förebyggande blodförtunning jämförs med de som inte fått blodförtunning, utfallen som studeras är venösa proppar och blödning. Här studeras även hur grad av albumin i blodet över tid korrelerar med risk för propp och blödning.

Resultat:

Studie I: Vi fann bland 12 106 inkluderade patienter att warfarinbehandling med god kvalitet jämfört med ingen blodförtunnande behandling medförde nästan halverad risk för stroke pga. blodpropp. Kostnaden för strokeskydd var en nästan 30% ökad risk för blödning med warfarinbehandling. Blödningsrisken var betydande (oavsett behandling eller ej) i CKD stadium 5-5D, här var allvarlig blödning mer än dubbelt så vanligt som stroke.

Studie II: Bland 2453 inkluderade patienter var DOAK associerat med lägre risk för blödning jämfört med warfarinbehandling av god kvalitet, men strokerisken skiljde sig inte mellan behandlingarna.

Studie III: 2379 patienter med warfarinbehandling inkluderades. Studien visade att risken för framför allt blödning, men även för stroke, minskade med förbättrad kvalitet på warfarinbehandlingen.

Studie IV: Bland 95 inkluderade patienter med nefrotisk syndrom drabbades 7,4% av venös propp och 18% av blödning, 4% allvarlig blödning. Förekomsten av utfall skiljde sig inte mellan de som fick förebyggande blodförtunning och de som var obehandlade. Gruppen som fick behandling hade troligen högre grundrisk för propp, varför det är svårt att uttala sig om behandlingen ändå gjorde nytta eller ej. Risken för både venös propp samt blödning ökade flerfaldigt vid tid med lågt albumin i blodet (s-albumin<20g/L).

Slutsatser:

Warfarinbehandling är associerat med en lägre risk för stroke på grund av blodpropp hos patienter med förmaksflimmer och CKD stadium 3-5D. Risken för blödning ökar dock av warfarin, en risk som redan är hög hos patienter med CKD, framför allt i stadium 5-5D. Blödningsrisken kan minskas med förbättrad kvalitet på warfarinbehandlingen. DOAK ger minskad risk för blödning jämfört med warfarin och verkar vara ett attraktivt alternativ, även hos dialysbehandlade patienter. Frågan kvarstår dock om blodförtunnande alls ska ges vid CKD 5-5D, på grund av den höga blödningsrisken. Enbart RCTs kan besvara denna fråga. Tills vi har bättre svar bör blodförtunning inte användas rutinmässigt vid förmaksflimmer och CKD 5-5D. Risken för venös propp och blödning är hög vid nefrotiskt syndrom och risken ökar vid tid med S-albumin<20g/L. Frågan om förebyggande blodförtunnande behandling är indicerad vid nefrotisk syndrom kan inte besvaras av vår studie, även här behövs en RCT.

Introduction

The kidneys produce almost 180 liters of primary urine each day at capillary pressures higher than in any other organ in the human body (1). It really is fascinating how these small organs, who are under such a tremendous workload, for most people will maintain their capacity year after year. It is hardly surprising that for some, the kidneys will eventually fail, and when they do, if left untreated, this is associated with high morbidity and mortality.

Chronic kidney disease

Chronic kidney disease (CKD) is defined as evidence of >90 days of decreased glomerular filtration rate (GFR), kidney damage or abnormalities detected by histology, imaging and/or laboratory work up including urine samples (2).

Epidemiology

The burden of chronic kidney disease varies depending on geographical areas and age-spans and is overrepresented in low- and middle-income countries and in ageing populations. The global estimated prevalence of CKD is 3-18% and continuously growing (3-6). A Swedish study found that 6% of patients accessing healthcare in Stockholm had CKD when defined as eGFR<60ml/min/1.73m^2 (7). Even though mortality in kidney failure, previously called end-stage kidney disease, is declining due to improved structural care, CKD is predicted as the 5th most common cause of death in 2040 by the Global Burden of Disease studies (8). More women than men have CKD but even so, females seem to have better prognosis and less risk of progressing to kidney failure or dying (9, 10). Important risk factors for progressive CKD, besides age, are diabetes mellitus and hypertension (5, 11). In Sweden, the most common causes of progressive kidney disease leading to kidney failure are glomerulonephritis, diabetic nephropathy, hypertensive nephrosclerosis and adult polycystic kidney disease (12).

Measurement and estimation of kidney function

GFR, the rate of which the glomeruli in the kidney filter the plasma, can be either measured or estimated. Decreased GFR is defined as <60ml/min/1.73m^2 and can be estimated (eGFR) with equations based on endogenous substances, in particular serum-creatinine (SCr) (13).

Traditionally the Cockcroft Gault (CG) equation has been used for estimating GFR. CG was not developed using standardized creatinine assays and has a tendency of overestimating GFR. Equations developed more recently use standardized creatinine assays. The most widely used are Modification of Diet in Renal Disease Study Group (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (14, 15). The Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommends the CKD-EPI equation, alternatively equations with even better accuracy (2). Estimating GFR by SCr ($eGFR_{Cr}$) has limitations since creatinine derive mainly from muscles and subsequently is affected by body constitution and also by diet. Since individuals differ in size, $eGFR_{Cr}$ generally is indexed to a body surface of 1.73m^2 and presented as ml/min/1.73m^2. An individual's non-indexed GFR is interesting in children and is traditionally used for drug dosing purposes, especially if the person's body or muscle constitution is considered deviant. However, KDIGO states that estimating GFR for drug dosing purposes is not well studied and a comparison of indexed- and nonindexed GFR showed no relevant differences (16). If greater accuracy is needed, GFR can be estimated by equations combining SCr and another endogenous substance called cystatin C. eGFR based on solely cystatin C ($eGFR_{Cy}$) is generally not more (or less) accurate than $eGFR_{Cr}$ but can be more expensive and should be used if $eGFR_{Cr}$ is thought not to be reliable. Important error sources for cystatin C are concomitant corticosteroid treatment, thyroid abnormalities, inflammation and smoking (17). The Swedish Revised Lund-Malmö equations are developed in a Swedish setting and equations based on SCr or cystatin C or both are available. The equations have been validated several times and the SCr based equation is shown to be superior to CKD-EPI and MDRD, especially in an older population with GFR<30ml/min (18-20). Adding cystatin C improves performance of the equation.

When estimation of GFR by creatinine, cystatin C or both combined is not sufficient, GFR can be measured. This can be suitable for example if necessary to exclude CKD in presumptive kidney donors or if several confounding factors are present. The golden standard of measured GFR is measuring the renal clearance of continuously infused inulin (21). Inulin is an exogenic polysaccharide freely filtered, not protein bound nor secreted or reabsorbed in tubule. This procedure is time consuming and expensive. There is evidence that renal- or plasma clearance of other exogenic substances with the same characteristics as inulin are sufficient to measure GFR- renal clearance of 51Cr-EDTA or iothalamate and plasma clearance of 51Cr-EDTA or iohexol. Measured GFR comes with both random- and systematic errors.

GFR categories and nomenclature

CKD GFR categories according to KDIGO guidelines are presented in **Figure 1.** The term advanced CKD refers to G4 and G5/G5D. Presence and quantity of albuminuria added to the GFR categories is used for prognosis in patients with CKD. Low GFR and high degree of albuminuria is associated with very high risk of progression to kidney failure, death and in particular cardiovascular death (2).

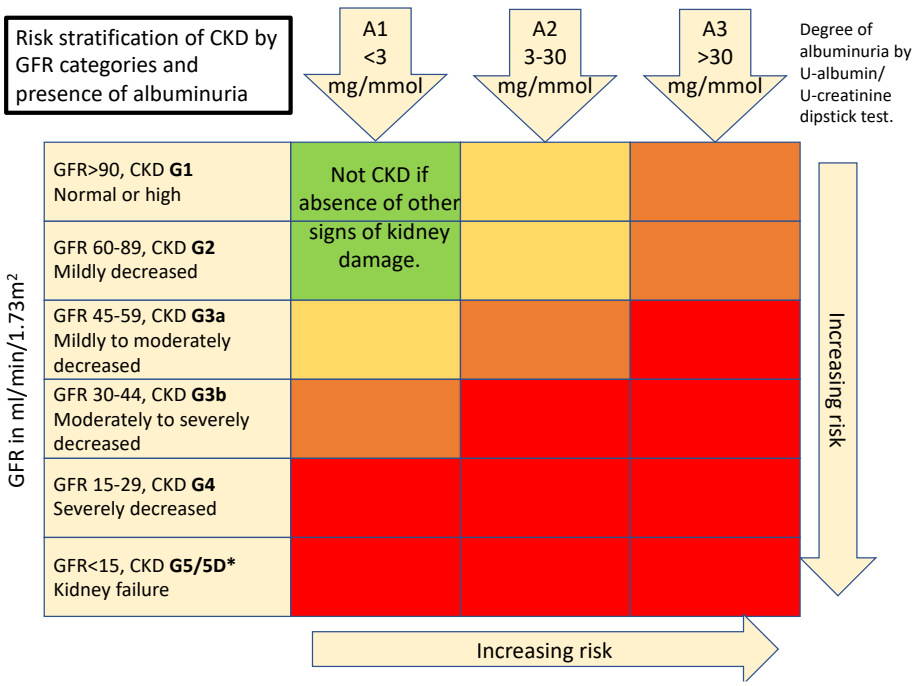

Figure 1. Figure describing CKD categories and risk of major outcomes such as progression of CKD, progression to kidney failure, death and cardiovascular mortality (2). Green= low risk, yellow= moderately increased risk, orange= high risk, red= very high risk. Adapted from KDIGO 2012 with permission.
*G5D= Kidney failure, on dialysis

Symptoms

When mild or moderate, chronic kidney disease is a “silent” disease, and symptoms such as fatigue, severe hypertension and anemia usually don’t unravel until GFR is <30ml/min (22). Progressive disease is often associated with volume overload, acidosis, severe hyperkalemia and other electrolyte derangements. Mineral and bone disorder (MBD) will develop and contribute to significant morbidity and mortality. Other symptoms of uremia such as gastrointestinal symptoms, anorexia and torturous pruritus can be devastating (23). If left untreated, kidney failure ultimately leads to death.

Treatment

Treatment of CKD should primarily focus on treating the underlying disease, for example immunomodulating therapies for glomerulonephritis. In preventing the progression of CKD, optimizing the therapy of diabetes mellitus and hypertension is crucial. The use of renin-angiotensin-aldosterone (RAAS)-inhibitors and introducing a sodium-glucose cotransporter-2 (SGLT-2)-inhibitor as well as dietary and lifestyle measures can furthermore preserve kidney function (2, 24).

Kidney replacement therapy and conservative uremic care.
A goal for each individual with progressive CKD is, in agreement with their physician, to decide on treatment strategy if or when kidney failure and severe uremic symptoms develop. There are three such strategies; kidney transplantation, dialysis or conservative uremic care. Transplantation and dialysis are classified as kidney replacement therapy (KRT).

The first human renal transplant was performed by the Ukrainian surgeon Voronoy in 1933 (25). He anastomosed a kidney to the femoral vein of a young woman suffering from acute kidney injury due to mercury poisoning. Unfortunately, the kidney did not function due to blood group incompatibility. The first successful kidney transplant was performed in 1954 by Joseph Murray, J. Hartwell Harrison, John P. Merrill and others at Brigham Hospital in Boston. This time the donor and the recipient were identical twins and immunosuppression was therefore not necessary. The recipient lived for 8 more years after transplantation, his twin brother lived 56 more years. For this achievement, Murray received the Nobel prize of medicine in 1990. Today, kidney transplantation is the recommended treatment in kidney failure due to better survival, best quality of life and also the most cost-effective option compared to dialysis (12, 26). Approximately 400-450 transplantations are performed yearly in Sweden. At the end of 2022, there were 10569 patients in Sweden in KRT and 6391 (ca 60%) of them had a functioning kidney transplant.

However, not all patients with kidney failure are eligible for kidney transplantation. Older or frail patients with several comorbidities might not benefit from transplantation. The shortage of available kidneys from deceased donors is a distinguished problem worldwide (27). In many countries, the waiting time for a kidney transplant can be several years. Patients not suitable for kidney transplantation or waiting for a kidney transplant are offered dialysis. Dialysis removes waste products from the bloodstream using a filter. There are two different dialysis modalities: hemodialysis (HD) and peritoneal dialysis (PD).

The first hemodialysis treatment was performed by Kolff who in 1943 dialyzed a young woman with acute kidney injury for 12 hours (28). The woman unfortunately died due to vascular access complications. In 1960 Belding Scribner developed shunted cannulas which enabled repeated dialysis sessions without vascular access failure. One of his patients lived for 11 years in hemodialysis. Later on, M. J. Brescia and James Cimino developed the arterio-venous fistula in 1966 at the Bronx Veterans Administration Hospital, this made the external Scribner shunt obsolete. The vascular access is indeed central in hemodialysis and is preferably an arterio-venous fistula suitable for repeated cannulation; one cannula leading the blood from the patient through a filter (dialyzer) and one cannula leading the cleared blood back to the patient. Currently, hemodialysis can be performed at dialysis wards or at home with self-cannulation. Common hemodialysis frequency in Sweden is 3 times per week, usually 4-5 hours per treatment (12).

Peritoneal dialysis uses the unique properties of the peritoneum as a dialyzer. The dialysate solution is inflated into the abdomen by a permanent catheter, usually the Tenckhoff catheter, invented in 1968 (29). Waste products and water are exchanged through the peritoneum before the dialysate is deflated through the catheter. Peritoneal dialysis can be performed at home (or anywhere!), by daytime or by night. Dialysis is lifesaving but unfortunately also associated with substantial morbidity, mortality, and reduced quality of life. Mortality in dialysis treated patients is decreasing in Sweden, from almost 30%/year in 1991 to 18%/year in 2022 (12).

A review estimated that 2.6 million people worldwide received KRT in 2010 and calculated that the number will be more than doubled in 2030 (27).

Conservative uremic care with symptom management, without KRT, can be a suitable option for patients not eligible for transplantation, with short expected survival or patients who do not wish to receive dialysis (30).

The blood coagulation and haemostasis

The ability to transform liquid blood to solid clots and obtain haemostasis is the body's necessary defense to blood loss when the vessels are injured. The physiology behind haemostasis can be described by three steps: primary haemostasis, plasma coagulation and fibrinolysis.

Primary haemostasis

The first defense to vessel injury is smooth muscle mediated vasoconstriction. Second, the injured vessel wall exposes von Willebrand factor (vWF) and collagen which bind and activate platelets from the blood stream (31). Activated platelets transform and send out pseudopodia which covers the injured vessel wall like a blanket. Also, the platelet fibrinogen receptor glycoprotein IIb/IIIa transforms, binds fibrin and then another platelet can attach; aggregation is started. Activated platelets release granule, including "dense granule" containing the potent platelet activator agent adenosine diphosphate (ADP). This formation of a platelet plug is called the primary haemostasis. The activated platelets also become negatively charged, creating a surface important for binding of coagulation factors.

Plasma coagulation

The vessel injury also leads to exposure of Tissue factor (TF) on perivascular and epithelial cells. TF is a strong receptor (and cofactor) for the freely circulating factor VIIa (FVIIa) and when they encounter, the TF-FVIIa complex is formed (**Figure 2**). TF-FVIIa activates circulating factor IX (FIX) and factor X (FX) (31, 32). Activated FX(FXa) can activate its co-factor, factor V (FV), and form a prothrombinase complex on TF-bearing cells. This prothrombinase complex generates a small amount of thrombin from prothrombin and is called the initiation phase of the coagulation. Thrombin is responsible for the cleavage of fibrinogen to fibrin. Fibrin is the most important part of stabilizing and maintaining a clot. Equally important, thrombin also activates the mediators factor V, factor VIII and factor XI (FV, FVIII and FXI) on the activated platelet surface in the amplification phase. FV and FVIII, together with FXa and FIXa, respectively, cooperate to greatly enhance the thrombin formation during the propagation phase. FIXa and FVIIIa forms the tenase complex, responsible for activating FX, this can be amplified by FXI. FXa and FVa forms more prothrombinase complex leading to a "thrombin burst" (31, 32). These steps are often called the coagulation cascade. The basic model of this cascade was first presented in 1964, and is still valid, although refined (33). The coagulation is balanced by inhibitory processes, mostly feedback loops and actions of the endothelium, and the role is to limit the clot. The TF-VIIa-Xa becomes inactivated by tissue factor pathway inhibitor (TFPI), a feedback loop activated by FXa (34). Antithrombin inactivates several proteolytic enzymes in the coagulation cascade, including thrombin. Antithrombin prefer the free enzymes that are not yet in complexes, this way it limits the clot formation to the site of the injury, and prevents liberated enzymes to start new cascades (31). Thrombomodulin is an

endothelial receptor, when free thrombin encounters healthy endothelium, it binds to thrombomodulin. This complex can also bind and activate protein C. Activated protein C (APC), together with its co-factor protein S, inactivates FVa and FVIIIa.

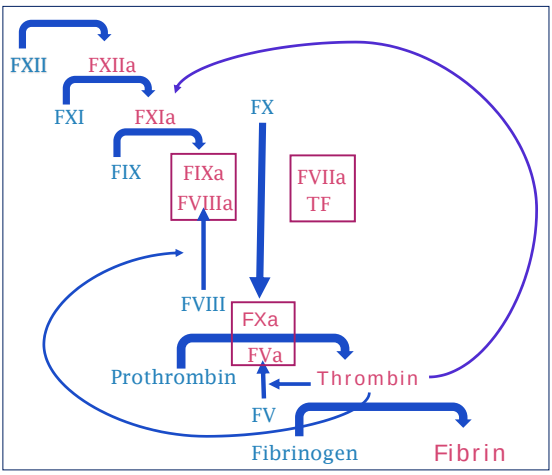

Figure 2. The coagulation cascade.

Fibrinolysis

Fibrin is degraded by plasmin, this resolves the clot. Plasminogen, an inactive precursor of plasmin, binds to fibrin and is activated by tissue plasminogen activator (tPA) released from for example endothelial cells and by urokinase-type plasminogen activator (uPA)/urokinase, produced by several cell types (35). Plasminogen activator inhibitor type 1 (PAI-1) which can inhibit fibrinolysis is often elevated with ageing and in patients with inflammation, diabetes, hyperlipidemia and the metabolic syndrome (36). One of the end products of degraded fibrin is D-dimer.

Prerequisite of thrombus formation – Virchow's triad

A platelet plug needs time to be reinforced by fibrin and grow. Often this does not happen since the clot gets washed away by blood flow. When the blood flow is somehow decreased, the clots possibility of lingering will increase. In the atrial auricula of the heart decreased blood flow is present, especially with concomitant atrial fibrillation. Furthermore, the space adjacent to the vein valves in the legs facilitates blood lingering. The three prerequisite of thrombus formation- disturbances in blood flow, altered haemostasis, hypercoagulability, and vessel/heart wall affection was described by Virchow >150 years ago, and is called the

Virchow's triad (37). One, or all, of these three prerequisites can explain the origin of most thrombi.

A thrombus can start migrating as an embolus. If formed in the leg veins as a deep venous thrombosis (DVT), it often breaks and ends up in the lung arteries as a pulmonary embolism (PE) (38). If formed in the left atrium of the heart, migration to the arteries of the brain is facilitated and can result in a thromboembolic ischemic stroke.

Coagulopathy in CKD

A paradox in CKD is the increased risk of both thrombosis and bleeding, a risk that increases with progressive uremia. The increased risk of thrombosis refers to both arterial vascular disease, thromboembolic- and atherosclerotic events, as well as venous thromboembolism (39-41). The high risk of thrombosis in CKD is due to high prevalence of shared traditional risk factors with the general population such as age, hypertension, diabetes and hyperlipidemia, but also due to independent risk factors attributable to CKD.

All mechanisms responsible for increased risk of thrombosis in CKD are not known, but some are described as follows: Altered hemodynamic qualities of the heart with low left atrial contractility and decreased emptying velocity (42). Blood vessel abnormalities with both enhanced atherosclerosis and arterial calcification leading to wall stiffness and higher pulse wave velocity are factors leading to endothelial damage with subsequent activation of the coagulation cascade (43). Chronic activation of coagulation occurs with elevated levels of FVIII and vWF as well as increased inhibition of anticoagulant responses including low levels of the potent platelet adhesion inhibitor nitric oxide (44, 45). Platelets in patients with CKD seem to be prone to aggregation, leading to increased clot formation, however the clots are not as functional, which in part can explain the increased risk of bleeding (46). The uremic platelet dysfunction is thought to be the most important explanation of the high risk of bleeding in patients with advanced CKD or on dialysis. Platelets in uremic patients have lower levels of platelet activators in their alfa-granulae, lower response to ADP, epinephrine and collagen, disturbed arachidonic acid metabolism and altered calcium mobilization causing dysfunctional activation and aggregation (47-49) Also, vessel-wall interaction is altered through anemia, causing disturbances of the laminar flow of the erythrocytes which normally pushes the platelets close to the vessel wall and by reduced expression of the platelet receptor GP1b leading to insufficient binding of vWF in uremic patients (49). Furthermore, repeated cannulation, frequent invasive procedures and

uncontrolled hypertension contributes to increased risk of bleeding in uremic patients.

The nephrotic syndrome

It's been described how Hippocrates saw that "when bubbles settle on the surface of the urine, it indicates disease of the kidneys" (50). In 1722 Theodore Zwinger III from Basel described a condition in children of "swelling of the whole body" called oedema or hydrops. These symptoms were linked to the kidney in 1770 when Richard Bright, UK, linked together proteinuria, oedema and kidney disease, established the entity of nephrotic syndrome. The big breakthrough that changed the course of the history was the introduction of percutaneous kidney biopsy in 1951 in both Denmark (Paul Iversen and Claus Brun) and the United States (Robert Kark and Bob Muehrcke). This was the start of understanding the different histopathological diagnoses responsible for the syndrome.

Nephrotic syndrome (NS) is defined as urine protein exceeding 3.5 g/day occurring in association with edema, hypoalbuminemia and hyperlipidemia (51). The glomerular barrier normally restricts passage of proteins from plasma to the urinary space. This barrier consists of fenestrated endothelial cells, the glomerular basement membrane and the podocytes with their slit diaphragm, and all three parts work together to restrict leakage of albumin and larger plasma proteins to the urine (1). The barrier is very complex and involves both size selective- and charge selective mechanisms helping to restrict large anionic proteins such as albumin. Damage to either part of the glomerular barrier can cause the proteinuria in NS. The oedema in NS is thought to be primarily driven by sodium retention (51).

The incidence of NS has been reported between 2-4 cases /100 000 patient-years (52, 53). NS is caused by primary or secondary glomerular disease, primary or secondary NS. In children the most common underlying diagnosis is minimal change disease (MCD), characterized of normal appearance of glomeruli in light microscopy (hence the name "minimal change") but with characteristic retraction of foot processes on electron microscopy. In adults, membranous nephropathy (MN) is the most common cause of NS (51). MN can either be a primary autoimmune disease or secondary, for example paramalignant, and is characterized by subepithelial immune complex deposits (1). Other diseases that can cause NS include focal segmental glomerulosclerosis (FSGS), diabetes, amyloidosis, and membranoproliferative glomerulonephritis (MPGN).

Thrombotic complications in the nephrotic syndrome

Nephrotic syndrome is associated with increased risk of thrombosis, mainly venous thromboembolism (VTE), although the association with increased arterial events is also recognized (51, 54, 55). The diagnosis membranous nephropathy (MN) has the highest risk of VTE, but increased risk is also seen in minimal change disease, MPGN and FSGS (56). Clinically evident VTE was reported in 7.2% of patients in a cohort with MN. Studies with radiological screening for VTE have shown up to 50% renal vein thrombosis (RVT) in MN (57, 58). Even though RVT is common at screening for VTE, in studies reporting clinically relevant VTE, PE and DVT are more common or as common in NS (56, 58). Mahmoodi et al. presented annual incidence of VTE in NS (primary and secondary) of 1.02%. If only considering the first 6 months, the risk was particularly high rendering an 10% incidence (56). This has to be compared with an annual VTE incidence of 0.1-0.2% in the general population (59). The cohort of Mahmoodi, which included both primary and secondary causes of NS, showed the highest annual incidence in MN (1.4 (95%CI 0.67-2.57)) and the lowest in diabetic nephropathy (0.58 (0.01-3.26)). VTE proneness in NS can, at least partly, be explained by increased production of prothrombotic factors and increased urine loss of antithrombotic factors. NS is associated with amplified liver synthesis of prothrombotic factors (FV, FVIII and fibrinogen) as well as increased access to arachidonic acid and enhanced platelet aggregation (60, 61). In addition, decreased fibrinolytic activity possibly due to elevated PAI-1 activity and low levels of antithrombin, protein C and S have been demonstrated (62, 63). There might also be local glomerular mechanisms present affecting the haemostasis, which could explain the proneness to RVT in NS (54, 64). The severity of hypoalbuminemia correlates with the degree of thrombotic risk and serum/plasma albumin levels <20–25g/L are considered as a risk factor for VTE in NS (65, 66) .

Manifest VTE is treated with LMWH or warfarin. DOAC is not recommended due to insufficient evidence of effectiveness and safety (66). Whether prophylactic anticoagulants (PAC) should be administered in NS with hypoalbuminemia is debated. So far, there are no RCTs comparing PAC and no PAC in NS. A recent Chinese RCT compared indobufen, a reversible platelet cyclooxygenase inhibitor, with warfarin (67). This study concluded that both exposures had similar effects on VTE prevention but indobufen conferred lower risk of minor bleeding. A handful small observational studies on prophylactic anticoagulants in NS (LMWH or warfarin) have been performed (68-72), only one had a control group. Recently, small observational studies without control groups and case reports on the use of DOAC in NS have also been published (71, 73, 74).

The 2021 KDIGO guidelines for glomerular diseases suggest PAC in NS patients with high risk of VTE and low risk of bleeding, especially in patients with membranous nephropathy, with serum albumin <20–25g/L (66).

Atrial fibrillation

Atrial fibrillation (AF) is the most common sustained arrythmia worldwide with an estimated current prevalence of 2-4% (75). A study from 2013 showed a prevalence of diagnosed atrial fibrillation of 2.9% in the Swedish population, patients in primary care excluded (76). Another Swedish study presented a prevalence of 2.5% from screening in a region of Northern Sweden; 3.9% in those older than 34 years. The prevalence increased with age; over 55 years 6% and in those older than 80 years 14% had AF (77). Another Swedish region in Northern Sweden, where patients in both primary and specialized care were included, had a documented AF prevalence of 4.7% in June 2020, reported in a recent cross sectional study (78). The real current prevalence number in Sweden, and in the world, is probably higher since the annual incidence and prevalence of atrial fibrillation is growing (79). The increase in patients with AF is probably not only due to enhanced detection but also to the ageing population and to the improved survival of patients with cardiovascular disease.

Atrial fibrillation is indeed an arrythmia of the elderly, with doubling incidence each decade after 60 years and the life-time risk is 1 in 3 (79). The prevalence in European patients aged >80 years was thought to be 10-17% in 2014 (80). Other risk factors of AF are hypertension, diabetes mellitus, heart failure, ischemic heart disease and chronic kidney disease (81, 82). Also, the prevalence is higher in men versus women and in Caucasians versus non-Caucasians (83).

Atrial fibrillation is a supraventricular arrythmia diagnosed by electrocardiographic absence of repeating P waves and irregular R-R intervals. The clinical consequence is ineffective atrial contraction which in turn can lead to symptoms of palpitations, dyspnea, and fatigue with stable- or sometimes unstable hemodynamics (75). A consequence of ineffective atrial contraction is atrial blood stasis with risk of clot formation that in turn can cause embolization and cardioembolic stroke. Atrial fibrillation increases the risk of ischemic stroke almost five-fold in a general population (84). This risk that can be decreased by 2/3 using anticoagulant medication (85). The cardioembolic stroke risk is however not homogenously distributed across all patients with AF, rather it

depends on other underlying risk factors. Therefore, the stroke risk for each individual with AF needs to be assessed to decide if anticoagulant therapy is warranted since the downside is increased risk of bleeding.

Atrial fibrillation in CKD

As mentioned, CKD is an independent risk factor for AF, and incidence increases with decreasing GFR. Approximately 20% of patients with GFR <45mL/min/1.73m^2 have AF and up to 27% of patients on dialysis have AF (82, 86). Also, a bidirectional relationship between AF and CKD have been demonstrated; CKD is a risk factor for AF, but AF is also a risk factor for new onset or progression of CKD (87).

Ischemic stroke and risk assessment

Risk factors for ischemic stroke, with and without CKD

Worldwide, stroke is the second-leading cause of death (88). A stroke is often ischemic but can also be caused by an intracerebral or subarachnoid hemorrhage. 87% of all incident strokes in Sweden reported to the Swedish Stroke Register in 2022 were ischemic (89). Globally, ischemic stroke constitutes of only 62% of all strokes and a larger proportion are bleedings (28% intracerebral and 10% subarachnoid), with a high proportion of intracerebral bleedings in low- to upper middle-income groups/countries (88). Ischemic strokes are mainly caused by cardiac embolism, artery-to-artery embolism and small vessel disease.

Risk factors for ischemic stroke in a general population are hypertension, diabetes mellitus, AF, carotid artery disease, heart failure, obesity, and dyslipidemia. These risk factors are also risk factors for progression/onset of CKD and many of them go bidirectional; CKD is a risk factor for hypertension and AF (82, 87, 90). CKD itself is also an independent risk factor for stroke. Hence, the causal pathway is complex. The risk of stroke in dialysis patients is reported 3.1-9.5/100 patients-years, which is up to 7 times higher than in a general population (91). It's been suggested that AF in advanced CKD is not an as strong risk factor for ischemic stroke as in the general population (92). The attributable risk of AF in CKD is, however, still evident with approximately 3 times higher risk of stroke in a CKD population compared to 5 times in the general population (93, 94). There are many non-traditional risk factors for stroke in the CKD population; these are thought to include features of uremia, oxidative stress, mineral and bone disorder with vascular calcification in CKD as well as dialysis related

factors with chronic inflammation, variability in blood pressure and decline in cerebral blood flow during HD (95).

Stroke risk assessment in atrial fibrillation

Stroke risk in AF can be assessed by different scoring systems (96). $CHADS_2$ was developed 2001 by combining two older scoring systems, AFI and SPAF, giving 1 point for Congestive heart failure, Hypertension, Age>75 years, Diabetes and 2 points for previous stroke or TIA (97). $CHADS_2$ performed better than its precursors but was refined in 2010 by adding points for vascular disease, female sex, age>65 and 2 instead of 1 point for age>75, creating CHA_2DS_2-VASc, with higher C-statistics (how well a risk scoring system can predict an outcome ranging 0.5-1.0 where 0.5 indicates the prediction is no better than chance and 1.0 is optimal prediction) than $CHADS_2$ (98).

The ATRIA stroke risk score was published in 2013, this scoring system adds points for proteinuria and eGFR<45ml/min and their internal- and external validation showed better C-statistics than $CHADS_2$ and CHA_2DS_2-VASc (99).

GARFIELD-AF is a prediction tool developed in 2016 and can be used for predicting both stroke, death, and bleeding (100). This gives a prediction based on different weights of age, previous stroke and bleeding, congestive heart failure, race, chronic kidney disease, and oral anticoagulants at enrollment. Compared to $CHADS_2$ and CHA_2DS_2-VASc the GARFIELD prediction tool performs better.

The ABC (Age, Biomarkers, Clinical history)-AF-stroke score, a biomarker based prediction tool is one of the newest clinical scoring systems that too performs better than CHA_2DS_2-VASc (101). Biomarkers included are plasma levels of NT-proBNP (N-terminal pro-B-type natriuretic peptide), cardiac troponin T, and growth-differentiation factor 15.

Even though there are several scoring systems performing better than CHA_2DS_2-VASc, the European Society of Cardiology guidelines do recommend this in clinical practice due to its simplicity. The scoring systems generally don't perform well in the setting of CKD. Adding additional points for CKD to $CHADS_2$ and CHA_2DS_2-VASc did not improve their predictive value (102). The scoring systems $CHADS_2$, CHA_2DS_2-VASc, ATRIA, AFI, and GARFIELD have been evaluated in a Swedish cohort; SCREAM (Stockholm CREAtinine Measurements) (103). In this study a modified-$CHADS_2$, adding more points with increasing age as well as weighting previous stroke higher, performed

best across all GFR stages; C-statistics 0.78, 0.73 and 0.74 in mild-, moderate and severe CKD respectively, whereas the CHA_2DS_2-VASc hardly performed better than chance in severe CKD, C-statistics 0.58 (104). A consensus report from KDIGO guidelines states that it is difficult to recommend any prediction tool in the advanced CKD population, due to poor performance of the tools and also due to the fact that this population has been excluded from the large anticoagulant trials (95).

Anticoagulant therapy

The history of the substances that still are the cornerstone in antithrombotic treatment started over a century ago and is truly fascinating.

Heparin

James McLean, a medical student at the Johns Hopkins medical school, US, became famous for his discovery by serendipity of the anticoagulant properties of animal tissues in 1916, paving the way for discovering heparin (105). McLean was trying to purify what he thought was a pro-coagulant substance from dog-liver, cephalin, but he soon discovered that aged cephalin became anticoagulant. While McLean continued to study cephalin, his supervisor Howell, together with another medical student Emmet Holt, extracted another compound from liver, which was water soluble, and we know it today as heparin. In 1935, the swede Erik Jorpes purified heparin and confirmed its structure as a highly sulfated glucosaminoglycan. The same year another swede, Clearance Crawford used Jorpes' purified heparin to prevent venous thrombosis (105). The unfractionated heparin (UFH) is still in use today, accompanied by low-molecular weight heparins (LMWH) with easier administration and prolonged treatment effect. Heparins work through catalyzing an enhancement (1000-2000 times) of antithrombin which in turn inhibits thrombin and activated FX. Heparins are administered intravenously or subcutaneously and are inevitable in several percutaneous and surgical procedures to prevent clotting as well as in catheters and tubes for plasma. Notably, UFH and LMWH have an important role in the treatment and prevention VTE (106).

Warfarin

Farmers in North America in the 1920's experienced how their cows died due to internal bleedings. Soon, the mysterious bleedings were linked to spoiled batches of sweet clover. In 1933 a farmer, Ed Carlsson, drove a dead cow 200 miles in a blizzard to the University of Wisconsin

Agricultural Station. He presented the problem to Karl Link, who started to purify the anticoagulant substance in sweet clover and discovered coumarol (107). Link also showed that vitamin K completely reversed the actions of sweet clover and dicoumarol, developed from coumarol. In 1942 dicoumarol was used for treatment of thrombosis for the first time. However, it was considered weak and unreliable why Link tested numerous derivates of coumarins. Soon he discovered warfarin, 4-hydroxycoumarin, which was first used as rat poison. Warfarin was introduced for commercial use in humans in 1954. It became famous when the US president D. Eisenhower was given the substance when he suffered from myocardial infarction (108).

The first randomised controlled study of warfarin versus placebo in the treatment of pulmonary embolism, presented in 1960, showed dramatic effects of reducing recurrent VTE and death in the active arm (109). In 1974, the vitamin K dependent clotting factors (thrombin, VII, IX and X, protein C and S) were discovered elucidating the anticoagulant properties of warfarin; blocking the enzyme vitamin K epoxide reductase (110). By this blockage, warfarin inhibits regeneration of vitamin K, which is necessary for the gamma-carboxylation of the vitamin K dependent factors and their subsequent binding to phospholipids (111). A meta-analysis of 6 RCTs by Hart in 2007 concluded a 60% risk reduction of ischemic stroke with warfarin compared to placebo in atrial fibrillation (85). Warfarin, and
other vitamin K-antagonists, VKA, need to be monitored due to their narrow therapeutical window, and are affected by dietary vitamin K and have many important drug interactions. In several fields their use has been replaced by direct oral anticoagulants (DOACs). However, warfarin is still the drug of choice for patients with mechanical prosthetic heart valves or moderate/severe mitral stenosis, to breastfeeding women, patients with antiphospholipid antibody syndrome and in nephrotic syndrome (96, 106).

Warfarin treatment quality
Warfarin effect is monitored by the prothrombin complex international standardized ratio (INR), where the optimal INR range is often set between 2-3. The treatment quality can be assessed by a method presented by Rosendaal; a daily INR value is estimated by interpolating a patients available INR measurements (112). The percentage of INR-values and interpolated values within range is the time in therapeutic range, TTR. TTR ≥70% has been demonstrated to reduce the risk of adverse events (113). Patients with CKD, especially patients on dialysis, often display poor TTR, with INR values which more often are

subtherapeutic rather than supratherapeutic (114-117). Sweden is renowned for its high TTR (≥70%) in a general population (118, 119).

Vascular calcification and calciphylaxis
Vascular calcification is common in patients with chronic kidney disease, especially in patients on dialysis, and is associated with increased mortality (120). The pathophysiology of the calcification process is not fully clarified but is probably due to disturbed balance between calcification promotors and inhibitors, possibly also driven by chronic inflammation. Matrix Gla protein (MGP), produced by vascular smooth muscle cells, is, in its carboxylated form, a strong calcification inhibitor, a carboxylation which is vitamin K-dependent (121). Dietary vitamin K deficiency as well as vitamin K antagonists (VKA) including warfarin can thus be associated with increased risk for vascular calcification (122).

Calciphylaxis is a special consideration of vascular calcification. A rare but dreaded condition caused by arteriole calcification leading to painful necrosis of dermis and subcutaneous tissue. Calciphylaxis mainly affects patients on dialysis (123). The true incidence is not known, and reported incidence differs from 0.04 - 4% per year in patients with hemodialysis (123-125). Calciphylaxis in kidney failure is often fatal, with mortality rates between 45-80% per year (126-128). The development of the microvascular calcification in calciphylaxis is thought to involve the same calcification process as described above and includes decreased calcification inhibition by MGP. Vitamin K antagonists, such as warfarin, can increase the risk of calciphylaxis by 3-13 times (129-131). Other risk factors for developing calciphylaxis include kidney failure, diabetes mellitus, obesity, hyperphosphatemia and hypercalcemia. There is no proven effective treatment of calciphylaxis. Risk factors such as warfarin treatment and high dose calcium and vitamin D should be withdrawn. The vasodilatory and antioxidant agent sodium thiosulphate is often tried as treatment. A meta-analysis has shown it might attenuate the progression of calcification, but no RCTs have been published proving its efficacy (130, 132). Treatment attempts with vitamin K supplements have been reported (133).

Direct oral anticoagulants (DOAC)

Due to the many limitations with warfarin, the work of developing new non-vitamin K dependent agents proceeded. In 2003 the first RCT of a direct thrombin-inhibitor in atrial fibrillation, Ximelagatran, was published (134). It was proven non-inferior to warfarin in stroke prevention but was soon withdrawn due to hepatotoxicity. However, this was the start of a new era of the new oral anticoagulants (NOAC), an acronym now replaced by DOAC.

Dabigatran was launched next in line in 2009, a direct thrombin inhibitor that received indication for stroke prevention in AF after the RE-LY trial (135). Dabigatran, 110 or 150mg BID (twice daily), was non-inferior compared to adjusted dose warfarin, mean TTR 64%, regarding stroke or systemic embolism. Dabigatran 150mg BID was also superior to warfarin regarding stroke prevention, with similar rates of major bleeding but increased risk of gastrointestinal (GI) bleeding. The rate of intracerebral hemorrhage was reduced in both dabigatran regimens.

Rivaroxaban, a direct FXa inhibitor, was introduced as stroke prophylaxis in AF by the ROCKET-AF trial in 2011 (136). Rivaroxaban 20mg OD (once daily) compared with dose adjusted warfarin, mean TTR 55%, was non-inferior regarding the primary outcome stroke and systemic embolism and there was also no significant difference in major bleedings.

The ARISTOTLE trial was also published in 2011 where apixaban, another direct FXa inhibitor was compared with dose adjusted warfarin, mean TTR 62% (137). Apixaban was superior to warfarin in stroke prevention, also less bleedings and death were seen.

Edoxaban is the most recent DOAC that achieved indication in AF though the phase III ENGAGE AF trial (138). This direct FXa inhibitor in doses 60 or 30mg OD, was compared to dose adjusted warfarin, mean TTR 65%. Both doses were non-inferior to warfarin regarding stroke prevention, although 30mg actually showed higher rates of stroke compared to warfarin, and less bleedings and death were seen.

Today, use of both the FX-inhibitors apixaban, edoxaban and rivaroxaban and the thrombin-inhibitor dabigatran is widely accepted. DOACs as thromboembolic prophylaxis in AF have been proven at least equally safe and effective as warfarin, have less interactions, faster onset and do not have to be monitored (135-138). No head-to-head trials have been performed comparing the DOACs. A meta-analysis of the four DOACs compared to warfarin showed less all-cause stroke, driven by less hemorragic strokes but equal effect on ischemic stroke (139). Further, DOAC showed less death and less major bleedings. DOAC is also mainly preferred for the treatment and prophylaxis of venous thromboembolism (106).

Anticoagulants in atrial fibrillation and concomitant CKD

The use of oral anticoagulants (OAC) for patients with high risk of thromboembolic events in CKD G1-G3 is not controversial. These

patients were included in the warfarin RCTs in the 90thies and the more recent DOAC trials (85, 135, 137, 138). For patients with G1-G3 DOACs are preferred before warfarin mainly due to lower risk of intracranial bleeding.

Warfarin has traditionally been the drug of choice in patients with eGFR<30ml/min/1.73m^2. Clinical experience of DOACs is growing in G4 due to EMAs (European Medicines Agency) and FDAs (United States Food and Drug administration) approval of DOAC (with some exceptions). These approvals were mainly based on observational data, even though a few patients with GFR 29-25 ml/min/1.73m^2 (G4) were included in ARISTOTLE. No RCT has specifically investigated OAC in G4. A meta-analysis including both available data from the pivotal DOAC trials as well as large observational studies favors the use of DOAC compared to warfarin in G3-G4 regarding risk of ischemic stroke and intracranial bleeding (140).

DOACs are not yet approved in G5-G5D in Europe nor in the US, although there is an FDA label on apixaban for GFR<15ml/min through dialysis in the US, and therefor data on DOAC versus warfarin in G5 are limited. Weir et al. showed no difference comparing rivaroxaban and warfarin regarding the risk of stroke- or major bleeding in G4-G5 (141).

Data on warfarin compared to no anticoagulants in patients on dialysis are conflicting and no RCTs has been completed so far, although the DANWARD as well as AVKDIAL RCTs are currently recruiting patients. The spectrum of observational data on warfarin and G5D covers both survival benefit as well as increased risk of ischemic stroke with warfarin (142-146). Recent meta-analyses suggest no prophylactic effect regarding stroke risk and more bleedings in warfarin treated patients on dialysis (147-149). On the contrary, another meta-analysis found no evidence of either harm or benefit of warfarin in patients on dialysis (150).

Recently three RCTs have been published comparing DOAC and VKAs. The VALKYRIE study was published in 2021 comparing rivaroxaban and dose adjusted VKA in 132 hemodialysis patients (151). Rivaroxaban compared with VKA, mean TTR 48% during the first 6 months, reduced the composite of fatal and non-fatal cardiovascular events and also conferred lower risk of major bleeding. Two non-inferiority trials comparing apixaban and VKA were published in late 2022 and early 2023. The RENAL-AF trial (n=154) compared apixaban and warfarin, mean TTR 44%, in patients on hemodialysis but was underpowered to draw conclusions on safety and efficacy (116, 117). However, the study results highlight the high risk of bleeding, which was 10-fold the risk of

stroke, in dialysis patients on OAC. Also, the trial attribute with important pharmacokinetic data since it included both standard and reduced dose apixaban; The 12 hour-area under the curve (AUC) for steady state of 5mg apixaban in G5D - HD, was almost two-fold of the AUC of patients with normal kidney function in ARISTOTLE but was similar to the AUC of patients on 5mg BID with mild to severe CKD. The 12-hour AUC of 2.5mg BID in G5 did not differ from the AUC of 2.5mg BID for patients with different degrees of impaired kidney function in ARISTOTLE. The AXADIA-AFNET 8 trial recruited 97 hemodialysis patients and randomised them to apixaban 2.5mg BID or the VKA phenprocoumon. This was also underpowered to show non-inferiority, although the authors conclude that there were no differences in safety or efficacy between the treatments (152). The largest conducted observational study comparing apixaban and VKA in G5D showed no difference in stroke rate but favored apixaban for avoiding major bleeding (153). Another observational study comparing rivaroxaban or dabigatran with warfarin showed increased risk of bleeding on DOAC (154).

Properties of the different available OACs are presented in **Table 1**. International guidelines on the usage of oral anticoagulants in G5D are inconsistent. American cardiology society guidelines suggest warfarin or apixaban are reasonable for patients with AF on dialysis (155). European society of cardiology guidelines do not have a recommendation (96). KDIGO does not recommend anticoagulation for dialysis patients with AF routinely (156). Furthermore, the guidelines recommend using scoring systems for bleeding risk assessment when deciding on OAC. However, the most common ones such as HASBLED (Hypertension, Abnormal Kidney and liver function, Stroke, Bleeding, Labile INR, Elderly and Drugs or alcohol) and ATRIA (the AnTicoagulation Risk factors in Atrial Fibrillation) do not perform well for patients on dialysis (45).

OAC associated nephropathy

The condition warfarin related nephropathy (WRN) was first described by Brodsky reporting findings of kidney biopsies of 9 cases of acute kidney injury associated with gross hematuria and supratherapeutic INR, revealing glomerular hemorrhage and occlusive red blood cells casts in tubule (157). These findings were confirmed and the diagnosis was accepted. WRN changed name to anticoagulant related nephropathy (ARN) when DOACs were introduced, and reports of similar cases emerged (158). The true incidence is unknown since patients rarely undergo kidney biopsy on this indication. Brodsky et al. later reported 20.5% cases of acute kidney injury in a cohort of 4006 patients who had

initiated warfarin treatment and where the raise in creatinine coincided with INR>3.

Table 1. Different properties and dosing of the OACs according to Swedish guidelines and European Medicines Agency (EMA)

Properties	**Apixaban**	**Rivaroxaban**	**Dabigatran**	**Edoxaban**	**Warfarin**
Administration	BID	OD	BID	OD	OD
Site of action	FXa	FXa	Thrombin	FXa	FII, FVII, FIX, FX, protein C and S
Half-life (h)	10-14	9-13	12-13	10-14	
Renal Clearance*	27%	36%	80%	50%	<1%
Removal with 4h dialysis*	7%	<1%	50-60%	9%	<1%
Dosing GFR>50	5mg BID**	20mg OD	150mg*** BID	60mg OD	Dosing by INR
Dosing GFR-≤50-30	5mg BID**	20mg OD	150mg *** BID	30mg OD	Dosing by INR
Dosing GFR 29-15	2.5mg BID	15mg OD	Not approved	30mg OD	Dosing by INR
Dosing GFR<15	Not approved	Not approved	Not approved	Not approved	Dosing by INR

*Adapted from Chan et al. (159) and www.fass.se
** Dose reduction 2 of the following: serum creatinine between 1.5 and 2.5 mg/dl, age ≥80 years, and body weight ≤60 kg
***110 mg BID if > 80years old or assessed high risk of bleeding

The Swedish healthcare- and quality registers

Sweden has a long tradition of healthcare- and quality registers making it possible to follow up, quality assure and conduct research on patients from birth until death. The National Board of Health and Welfare governs the 6 healthcare registers including National Patient Register (NPR), National Cancer Register, National Medical Birth Register, National Register of Care and Social Services for the Elderly and Persons with Impairments, National Dental Health Register and National Prescribed Drug Register (PDR). The National Cause of Death Register is also governed by The National Board of Health and Welfare. These registers have high to almost complete national coverage of people who have sought medical attention or deceased in Sweden. Diagnoses registered are identified by International Classification of Diseases (ICD) codes and the validation of these differs.

Furthermore, there are approximately 100 quality registers in Sweden, introduced the last two decades (160). These registers contain more

detailed individual-based clinical data than the healthcare registers about patients included, such as smoking status, laboratory work up or quality of life. Validity, coverage and completeness however differ. The Swedish personal identity number makes it possible to link these registers together (161).

Aims of the thesis

The overall aim of the thesis is improved care for patients with kidney disease and high risk of both thromboembolic disease and bleeding.

In specific:

- To investigate benefits and risks of oral anticoagulants in patients with atrial fibrillation and chronic kidney disease GFR category 3-5D
- To examine the role of warfarin treatment quality as a predictor for ischemic stroke and bleeding in atrial fibrillation and chronic kidney disease
- To investigate benefits and risks with prophylactic anticoagulation in nephrotic syndrome and elucidate risk factors for thrombosis and bleeding

Materials and Methods

Paper I-III

Paper I-III are observational register studies.

Included registers

Swedish Renal Registry (SRR) is a national quality register created 2007 by merging the Swedish Register for Active Uremic care (SRAU, started 1991) and Swedish Dialysis Data Base (SDDB, started 2002). The register has several parts, registering the quality of care of CKD, dialysis and transplantation (12). All Swedish nephrology units/departments report to SNR. The dialysis part had 92% coverage of patients on hemodialysis and 97% coverage of peritoneal dialysis in 2022. In the CKD part the coverage is approximated to 95% and all clinics report patients systematically from CKD G4 (some from G3). Over 80% of patients starting dialysis are previously known at a nephrology department.

The Swedish National Patient Register (NPR) is a one of 6 health registers governed by the National Board of Health and Welfare and has registered in-patient care since 1964 and specialized out-patient care since 2001. NPR is considered to have an almost complete coverage of hospital admissions and out-patient visits, registering ICD-10 codes and surgical procedure codes. An external review and validation of in-patient care diagnoses in NPR by Ludvigsson et al. showed a generally high validity of 85-95% (162). The positive predictive value of AF was 97%.

The Swedish Stroke Register (SR) is a quality register of acute stroke in Sweden (89). SR has a higher validity of the stroke diagnosis than NPR and also provides the correct date of the index stroke. Of all registered strokes in Sweden in 2020, 96% were found in NPR, 87% in SRR and 83% in both registers (163).

AuriculA is a Swedish quality register active between 2006-2018 that monitored patients with atrial fibrillation and oral anticoagulation, with a coverage in 2018 of 55% (164). Whole regions reported to AuriculA, with no evident selection bias. The register provides information of type and dosage of anticoagulant, ordination periods and INR for warfarin users.

The Swedish Prescribed Drug Register (PDR) is a national health register with complete coverage of all drug-dispenses at pharmacies in Sweden since 2006.

The Cause of Death Register (CDR) provides date of passing of a deceased in Sweden.

Power calculation

A power calculation for paper I was based on the Danish study by Olesen where the stroke rate was 6.4/100 patient-years in CKD and 5.6/100 patient-years in G5D (142). We estimated the stroke risk to 5% in the intended cohort. Olesen et al. found a 16-56% risk reduction of ischemic stroke with warfarin. The risk reduction of OAC in a general population is 66%. If power is set to 80% with a 5% significance level, a stroke risk of 5% in the untreated arm and a risk reduction of 30% to 3.5% stroke risk will require 2837 patients per treatment group. If the risk reduction is 50%, 903 patients per treatment group are required.

For paper II we also used data from Olesen et al. who saw a bleeding rate of 8.8/100 patient-years among patients on warfarin or/and aspirin or no treatment. Siontis et al. compared apixaban and warfarin in G5D and saw approximately 20 major bleedings/100 patient-years on OAC (153). For the power calculation we estimated the bleeding risk on OAC to 10%. Siontis et al. reported a 28% risk reduction of major bleeding on apixaban, HR 0.72 (0.59-0.87). If power is set to 80%, with a 5% significance level, a bleeding risk of 10% in warfarin arm and a risk reduction of 25% to a bleeding risk of 7.5% in DOAC arm will result in sample size required of 2003 per group. If power is set to 80%, with a 5% significance level, a bleeding risk of 15% in the warfarin arm and a risk reduction of 25% to a bleeding risk of 11.25% in the DOAC arm will result in a required sample size of 1270 per group.

Inclusion

Adult patients with eGFR<60ml/min/1.73m^2 collected from SRR with a concomitant diagnose of atrial fibrillation or atrial flutter (ICD-10 I48, ICD-9 427D) were included when both inclusion criteria were fulfilled before or within follow up time January 1st, 2009, until December 31st, 2018. Patients were excluded if evidence of being kidney transplant recipients (registered as kidney transplant recipient in SRR or ICD-10 Z940, ICD9 V42A or KAS0-KAS2). Signs of valvular atrial fibrillation defined as evidence of mitral stenosis or mechanical heart valve were also exclusion criteria (ICD-10 Z95.2, I05.0, I34.2, Q23.2). A patient was censored if diagnosed with valvular AF or kidney transplanted during

follow up. Included baseline characteristics and their sources are presented in **Table 2**.

All eligible patients with non-valvular AF (NVAF) and G3-G5D were included in the cohort in paper I. Time zero (t0) occurring when a patient had fulfilled both inclusion criteria before or wihtin follow up, at the earliest January 1st, 2009, and the latest December 31th, 2018. Paper II included the patients from paper I with treatment periods of warfarin from AuriculA or DOAC (apixaban, edoxaban, rivaroxaban and dabigatran) from PDR (**Figure 3**). In this paper, patients with evidence of long-term OAC use (defined as any OAC prescription 3-4 years prior inclusion) also were excluded. T0 in paper II occurred when inclusion criteria were fulfilled and a treatment period of warfarin or DOAC had started within, or before, follow up. Paper III included only patients with warfarin treatment periods from AuriculA and t0 occurs when the first INR-measurement is recorded.

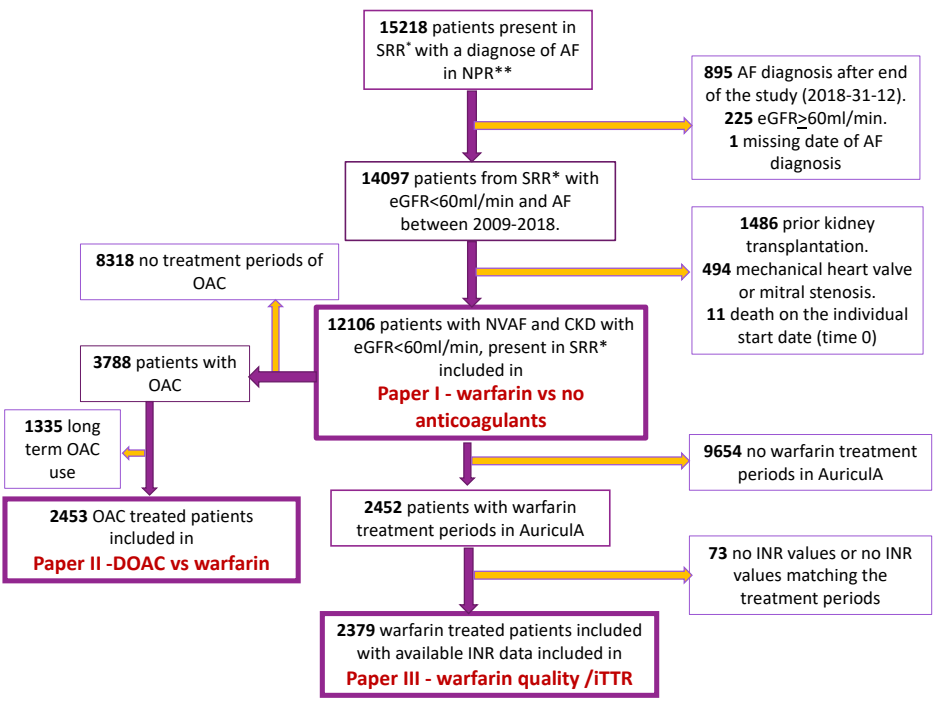

Figure 3. Steps of inclusion paper I-III
*SRR= Swedish Renal Registry, **NPR= The Swedish National Patient Register

Table 2. Full list of included variables and their sources paper I-III*

Medical history	**ICD-10**	**ICD-9 (from NPR[1])**
All cause stroke	NPR+SR[2]: I60, I61, I63, I64, I69	430, 431, 433, 434, 436, 438
Anemia	NPR: D50, D510, D513, D518, D519, D52, D53, D55, D560-562, D568, D569, D570-D572, D588, D589, D59-D64	280, 281, 282.C, 282.D, 282.E, 282G, 282X, 282W, 283, 284, 285
Cancer	C00-C26, C30-C41, C43-C58, C60-C97	140-208
Cerebral haemorrhage	NPR: I60-I61	430, 431
Chronic obstructive pulmonary disease	NPR: J43, J44	491C, 491W, 492, 496
Congestive heart failure	NPR: I110, I130, I132, I50	402, 404, 428
Dementia	NPR: F00-F03	290, 294B
Diabetes	NPR: E10-14	250
Excessive alcohol use	NPR: E244, F10, G312, G621, G721, I426, K292, K70, T51, Y90, Y91, K860, O354, Z714	291, 357F, 425F, 571A-D, 535D, 980, 760W
Gastrointestinal bleeding	NPR: I85.0, I98.3, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K661, K625, K920-K922	456A, 531A, 531C, 531E, 531G, 532A, 532C, 532E, 532G, 533A, 533C, 533E, 533G, 434A, 434C, 434E, 434G, 569D, 578A, 578X
History of fall	NPR: >2 occurrences of W00-W19	E88
Hypertension	NPR: I10-I13, I15	401, 402, 403, 404, 405
Intracranial bleeding	NPR+SR: 160-I62, S064-S066	430, 431, 432, 852
Ischemic heart disease	NPR: I20-I23, I241, I248, I249, I251, I252, I255, I256, I258, I259	410, 411, 412, 413, 414
Liver disease	NPR: K70-77, JJB, JJC,	570-573, JJB, JJC
Major bleeding	NPR+SR: I85.0, I98.3, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K625, K661, K920-K922, I60-I62, S064-S066, H313, H356, H431, H450, I312, J942, M250, N501A N939, N950, R04, R319, R319A, R589, T810, D629	285B, 430, 431, 432, 456A, 531A, 531C, 531E, 531G, 532A, 532C, 532E, 532G, 533A, 533C, 533E, 533G, 434A, 434C, 434E, 434G, 569D, 578A, 578X, 363G, 423A, 719B, 784H, 784W, 786D, 599H, 459A, 998B, 626G,
Myocardial infarction	NPR: I21, I22, I252	410, 412
Obesity	NPR: E66	278A
Other bleeding	NPR: H313, H356, H431, H450, I312, J942, M250, N501A, N939, N950, R04, R319, R589, T810, D629	363G, 423A, 719B, 784H, 784W, 786D, 599H, 459A, 998B, 626G, 285B
PCI	NPR: Z955	V434
Previous traumatic intracranial bleeding	NPR: S064-S066	852
Stroke or TIA	NPR+SR: I63, I64, I69, G45 (except 6454)	433, 434, 435, 436, 438, 362D
Transient ischemic attack (TIA)	NPR+SR: G45 (except G454)	435, 362D
Vascular disease	NPR: I21, I22, I252, I70-I73, I65	410, 412, 440-443

[1]NPR= The Swedish National Patient Register
[2]SR= The Stroke Register
[3]SRR= Swedish Renal Register
*SRR also provided eGFR ml/min/1.73m^2, Systolic and diastolic blood pressure, mmHg, BMI, body mass index, B-hemoglobin, g/L and U-albumin/creatinine, mg/mmol

Treatment periods

All treatments are treated as time-dependent covariates and updated when evidence of a change in treatment. Patients can thus change treatments several times during follow up.

Paper I
Warfarin treatment periods start- and stop date were collected from AuriculA. **No treatment** was defined as no dispenses of either warfarin in PDR or no treatment period in AuriculA. **Undefined treatment** periods started if evidence of a dispense in PDR of either DOAC or warfarin not matching an ordination period in AuriculA. The undefined period persisted the number of days the DOAC or warfarin dispense covered (1 tablet of warfarin per day) and an additional grace period of 6 months. Patients included in multidrug dispensing with DOAC had their treatment periods defined as number of days covered by dispense and a grace period of 1 week. Incident warfarin treatment was defined as no evidence of prior OAC treatment in AuriculA or PDR back from 2007, the patient is hence considered as OAC naïve.

Paper II
Warfarin treatment periods were defined as in paper I. **DOAC-treatment** periods started at dispense date and lasted for the number of days covering assumed standard pill use and an additional grace period of 30 days (4 if included in multidrug dispensing system). Undefined treatment was a period of no OAC or a period with warfarin from PDR where one dispense of warfarin was counted as 6 months of treatment plus 30 additional days. The undefined definition was used only for calculating incident OAC treatment. New/incident treatment was defined as no evidence of OAC within one year.

Paper III
Warfarin treatment periods were collected from AuriculA. However, in paper III, the treatment period from AuriculA also needed to have **concurrent INR-coverage**. The warfarin treatment period starts when the first INR value within an AuriculA ordination period is registered and is valid for 90 days, if the treatment is ongoing in AuriculA. A treatment period was prolonged if a new INR was collected within 90 days, otherwise it stopped until a new INR value was registered.

Kidney function status

eGFR estimated with MDRD formula was collected from SRR and classified in GFR categories 3-5D according to KDIGO guidelines, G3a

and G3b were merged. CKD G3: eGFR 30-59 ml/min/1.73 m², G4: eGFR 15–29, G: eGFR <15, G5D: on dialysis. Due to time updates, eGFR could decrease and G3 could switch to G4, to G5 and so on. Improved eGFR was disregarded.

TTR and individual TTR (iTTR)

TTR was calculated according to a method by Rosendaal where a daily INR is estimated by interpolating a patients available INR values (112). Time with INR within the range 2-3 is calculated and divided by total time and multiplied with 100, determining TTR (%) (**Figure 4**). TTR is presented in paper I-III in total, meaning that all patients time in range 2-3 (during valid warfarin treatment periods) is divided by total time with INR-coverage. In paper III, individual TTR (iTTR) for each patient is calculated and used as a time dependent covariate. ITTR is then updated at each new available INR and is based on the available and interpolated INR values the last 90 days (**Figure 5**). An iTTR-value corresponding to the first INR value in a treatment period is calculated by carrying forward the last recorded INR value before the period to the day before the new treatment period. If no such value exists, the INR value 1 is used.

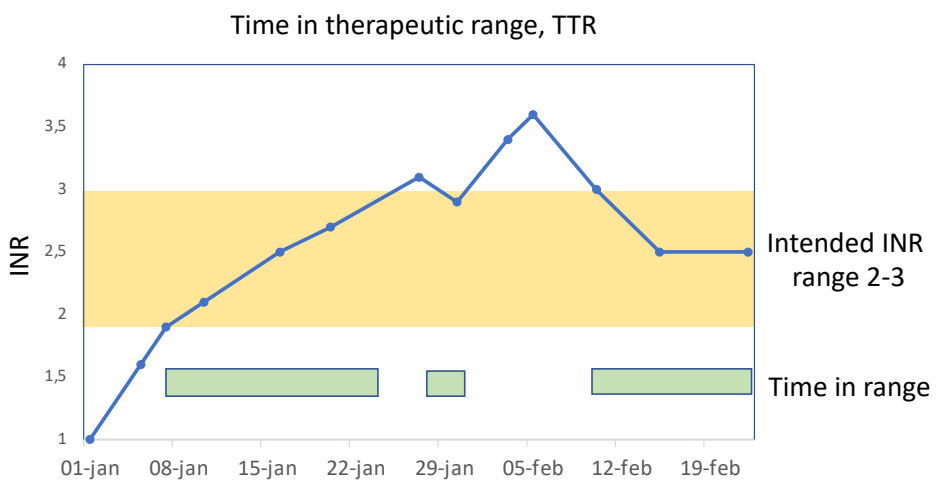

Figure 4. Calculation of TTR according to Rosendaal et al. where a daily INR value is estimated by interpolation of available measured INR values (blue dots). The percentage of the time in range, represented by the green boxes, (time in range/observation time) x 100, gives us the TTR (%).

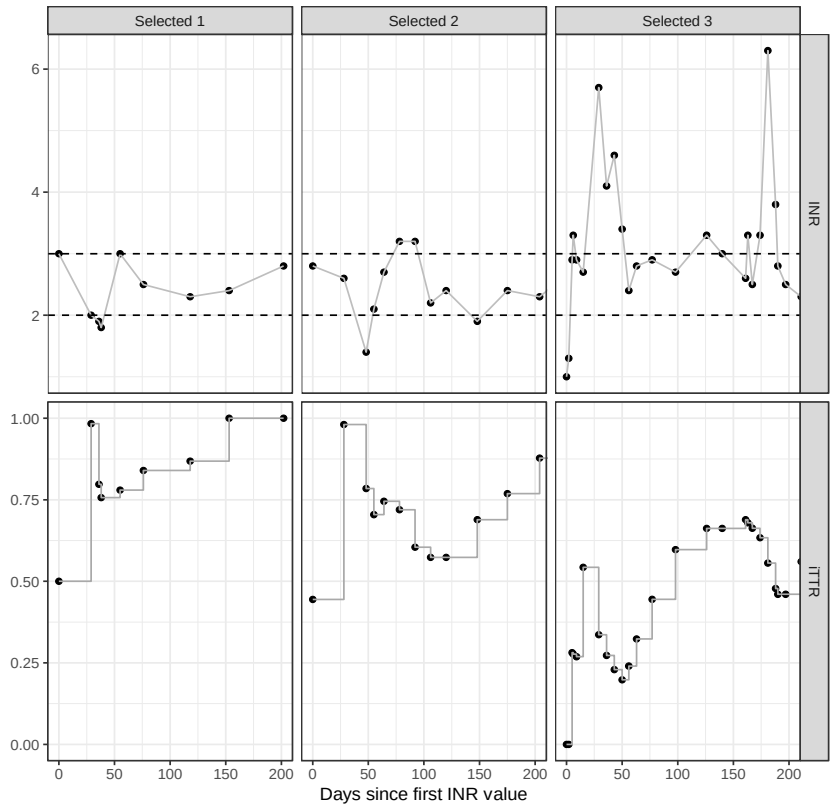

Figure 5. How INR and iTTR correlates in three selected patients.

Outcomes

Primary outcomes in paper I-III were ischemic stroke and major bleeding (intracranial, GI, or other) requiring inpatient care. All-cause mortality was a secondary outcome, in paper I there were also other secondary outcomes included (**Table 3**). Events occurring at t0 are registered as baseline characteristics, death on t0 leads to exclusion. Ischemic stroke was collected from SR or NPR. In the published paper I, strokes were only collected from SR. Due to surprisingly few events, an additional search was made in NPR and these ischemic strokes are added (when indicated) to data from paper I in this thesis. To avoid doublets of an index stroke, ischemic strokes from NPR are disregarded the first two weeks after t0 if there was a stroke at t0 or 14 days prior. In paper II-III, strokes were collected from SR and NPR. All outcomes were analysed in respect to current eGFR and current ongoing treatment. In paper III, outcomes were only counted if occurring during a period of INR-coverage. After the occurrence of an event, the patient is censored for this event, but remains in the cohort for other possible outcomes.

Table 3. Full list of outcomes and their sources paper I-III

Outcomes	
All-cause stroke and systemic embolism	NPR[1]: I60 RS: I61, I63, I64 NPR: I74
All-cause stroke	NPR: I60, RS: I61, I63, I64
Ischemic stroke*	NPR+SR[2]: I63
Haemorrhagic stroke	NPR: I60 SR: I61
Major bleeding*	Any of intracranial, gastrointestinal, or other bleeding
Intracranial bleeding	NPR:160 SR: I61 NPR: I62, S064-066
Gastrointestinal bleeding	NPR: I850, I983, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K661, K625, K920-K922
Other bleeding	NPR: H313, H356, H431, H450, I312, J942, M250, R04, N501A, N939, N950, R319, R58, T810, D629
All-cause mortality	Presence in the Swedish cause of death register
Myocardial infarction	NPR: I21, I22

[1]NPR= The Swedish National Patient Register
[2]SR= The Stroke Register
*Primary outcomes. **Bold outcomes=** present in all papers I-III

Statistics

Data was processed using R 4.2.0-4.3.0 (R Core Team 2022-2023). Baseline characteristics were described with count (percentage) and numerical variables: median (1st quartile Q1 to 3rd quartile Q3). Primary and secondary outcomes were analysed with respect to current treatment except in paper III where they were analysed in respect to current iTTR. Treatment, iTTR calculated in a 90-day window, and other covariates are time-varying and updated at each recorded change. Covariates adjusted for in all papers were sex, age, GFR category, years from study start and for any prior events of the following: prior stroke or TIA, major bleeding, congestive heart failure, diabetes mellitus, hypertension, vascular disease, myocardial infarction, PCI and excessive alcohol use. All quantitative variables were used in models as restricted cubic splines with three knots except iTTR that was modelled linearly. Crude numbers are presented with event rates and 95% Confidence Intervals (95% CI). Kaplan-Meier curves illustrate the cumulative incidence of events. Cox Proportional Hazards Models are used for all adjusted analyses after assuring fulfillment of the assumption of proportional hazards.

Models used in paper I

Main analysis

Warfarin versus no treatment in all patients, adjusted for the already mentioned time-dependent covariates. Also, subgroup analyses with interaction for G3, G4, G5 and G5D were performed.

Sensitivity analyses
Warfarin versus no treatment, in all patients and in G3-G5 and G5D separately. Additional time-dependent covariates of clinical relevance were added. For patients in G3-G5 blood pressure, S/P- albumin and B-hemoglobin were added in addition to mentioned covariates, for G5D dialysis modality was added. Also, incident warfarin treatment and no anticoagulant treatment was compared in OAC naïve patients with same models and adjustments as in main analysis.

Models used in paper II
Main analysis
DOAC versus warfarin adjusted for the already mentioned time-dependent covariates in all patients. Subgroup analyses added GFR category interaction (G3, G4 and merged G5-5D).

Due to unexpected high hazard of death for DOAC compared with warfarin, an additional analysis was carried out *a posteriori*—cumulative incidence of death within 7 days after major bleeding (possible fatal bleeding).

Sensitivity analyses
OAC naïve patients (no OAC the last 365 days) were included in a sensitivity analysis comparing new/incident DOAC and warfarin treatment, this treatment period only, no longer than 2 years. Balance primarily was sought on GFR category and age. Secondarily balance was sought on previous occurrence of stroke/TIA, intracranial bleeding, gastrointestinal bleeding, diabetes mellitus and myocardial infarction. GFR category was unevenly distributed among warfarin (n = 699) and DOAC (n = 457) in this cohort. Optimal matching was used, allowing comparison clusters containing up to 10 controls to one case, or up to 3 cases to one control (each cluster including either exactly one case or exactly one control). Cases receive a weight of one, and controls receive a weight so that the clusters are balanced (i.e. a weight ranging from 1/10 to 3). These weights are used in a Cox regression along with the clusters to obtain robust standard errors. Matching was performed using Mahalanobis distance. Covariates could be added if the overall balance seemed to improve and without considering outcome data. This resulted in using all but prior myocardial infarction as matching covariates, and 564 of the warfarin controls weighted to 457.

Two additional sensitivity analyses were carried out using the same model as main analysis with the same adjustments but excluding the heterogenous group of G5D. The first, comparing DOAC and warfarin in

G3-G5. The second comparing only correctly dosed apixaban and warfarin in G3-G5. Correctly dosed apixaban was defined as appropriately reduced dose to patients fulfilling 2 of 3 criteria in G3: age ≥80 years, body weight ≤60 kg and serum creatinine ≥133 µmol/L, or correctly prescribed standard dosed if fulfilling ≤1 criteria. Correct dose in G4-G5 was deemed 2.5mg apixaban BID.

Models used in paper III
Impact of iTTR, modelled linearly, on outcomes was tested with Cox regression with same time dependent covariates as described above. The impact of iTTR< and ≥70 % was tested the same way: iTTR is again treated as a time-dependent covariate and is updated at each new available INR, <70 % means all time iTTR is <70 % and iTTR ≥ 70 % is all time when iTTR is at least 70 %. An individual can thus potentially move between the 2 groups defined and contribute time at risk in both groups at different times. An event experienced by an individual will be attributed to the group that the individual belongs to at the time of the event.

Paper IV

Material and inclusion

A retrospective chart review from three hospitals (Sundsvall, Sollefteå and Örnsköldsvik) in the county of Västernorrland, in northern Sweden.

A laboratory search identifying patients with urine-albumin/urine-creatinine ratio (U-alb/U-crea) >300mg/mmol or urine albumin (U-albumin) >3000mg/24 hours combined with serum- or plasma-albumin (S/P-albumin) <30g/L between January 1st, 2010, and July 31st, 2019. Measurement of S/P-albumin was performed with spectrophotometric method with reagent and calibrator from Roche. All patients' medical charts were analysed, and patients were eligible if S/P-albumin was <30g/L within 30 days of the urine sample (fulfilling NS laboratory criteria) and there is at least one more consecutive measurement of U-alb/U-crea or 24h urine-collection and S/P-albumin after fulfilling NS diagnose. Patients also needed to be in- or outpatients at one of three nephrology departments in Västernorrland and have a biopsy proven glomerular disease. Exclusion criteria were age <18 years, patients on KRT (including kidney transplant recipients) and patients on anticoagulants prior to NS diagnosis. Steps of inclusion is presented in **Figure 6**. Included patients were followed until remission, but minimum 365 days if remission was achieved within a year. Remission

was defined as two consecutive S/P-albumin >30g/L combined with U-alb/U-crea <300mg/mmol. Patients were censored if starting KRT or if prescribed anticoagulants due to other reasons than VTE prophylaxis. Patients' medical charts were reviewed for baseline data, exposure, and outcomes. All in- and out hospital medical records, excluding psychiatric records, were reviewed for outcomes.

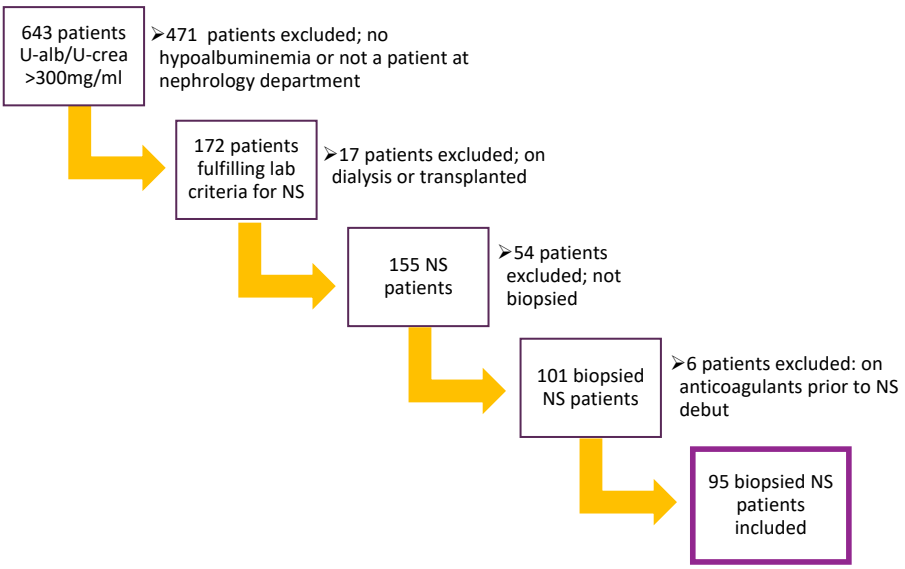

Figure 6. Steps of inclusion

Treatment

PAC was defined as oral anticoagulants or LMWH excluding antiplatelet therapy, used as primary prophylaxis of VTE during NS. Patients who had received PAC at any time during follow up ended up in PAC group.

Local guidelines for NS were recommending PAC for patients with S/P-albumin <20 g/L, using LMWH (low dose (<5000IU) or high dose (>5000IU) dalteparin at the physician's choice) followed by warfarin with target INR 2–3 if considered appropriate. DOAC was not recommended. For patients assessed having high risk of thrombosis, such as proven MN, a cut-off of S/P-albumin <25 g/L was used.

Outcomes

Clinically evident VTE, minor and major bleeding and death were primary outcomes. Arterial thrombotic events were secondary outcomes. Bleedings were divided into major and minor bleedings according to International Society on Thrombosis and Haemostasis (165, 166).

Statistical analysis

Baseline characteristics and frequency of outcomes with respect to treatment group were compared using Fisher's exact test for categorical variables and Mann Whitney U-test for continuous variables in IBM SPSS. P-values <0.05 were considered statistically significant. A sensitivity analysis was performed excluding patients with NS due to diabetic nephropathy. Event rates in two albumin intervals, S/P-albumin < and ≥ 20g/L, were calculated by estimating a daily S/P-albumin using a variation of the TTR method described by Rosendaal. Linear interpolation of available S/P-albumin measurements enabled assignment to one of the S/P-albumin categories each day. Event rates were calculated by dividing the number of events by the total time in each S/P-albumin interval. A 95%CI as well as incidence rate ratio (IRR) with 95%CI with was calculated for rates by Mid-P exact test (167).

Ethical considerations

Papers I-III are register studies approved by the Swedish Ethical Review Authority, registration number 2019-03289. Linked data collected from the registers makes it possible to follow a person from birth to death, and all diagnoses encountered in between. This threatens the personal integrity of included persons and data need to be treated with care and respect. We considered our study questions important and assessed that the results could help improve the care of patients on group level with minor harm on individual level. We collected only the necessary data to answer our study questions and all data were anonymized when accessed by researchers. Results are only presented on group level, minimizing the possibility to track individuals for both researchers and the public. Due to the large number of patients and data collected from the registers it was not possible to obtain personal consent.

Paper IV is a retrospective medical records study approved by the Swedish Ethical Review Authority, registration number 2019–04789. The need for personal consent was waived since the data collected was presented in aggregated form, no intervention was done and the potential harm or discomfort this might create was considered minor. Nevertheless, a medical records search is always an intrusion of the patient's private sphere. Data from a small and regional study needs to be presented with caution, even if data is anonymized, to ensure personal integrity. Anonymizing of data was achieved by coding all patients, the code key was then locked in at the institution. After finishing the project, the anonymized data have also been locked in the same way.

Results

Paper I-III

Cohort description

A cohort of 12106 patients with NVAF G3-G5D is the cornerstone of paper I-III; all these patients are included in paper I and are the base from where the cohorts in paper II-III are extracted (**Figure 3**). The main cohort of 12106 patients at inclusion is described in **Table 4**, as the total cohort, as separate GFR categories and the OAC naïve patients. In this cohort patients t0 (time zero) or time of inclusion is at the time when patients fulfill both inclusion criteria NVAF and eGFR<60ml/min/1.73m², independently of treatment. These patients can switch between treatment groups and are therefore not described in relation to treatment. In paper II and III, t0 is the patients first treatment period of DOAC or warfarin (paper II) or warfarin (paper III). These patients baseline data are therefor also described in relation to first treatment period of each treatment (**Table 5-6**). The distribution of GFR categories at t0 in each paper is presented in **Figure 8**. The mean age in all three cohorts was 77 years, and about 30% were female. Approximately 70% of patients on dialysis was on hemodialysis (paper I 71.1%, paper II 69.2%, paper III 65.2%), the rest had peritoneal dialysis.

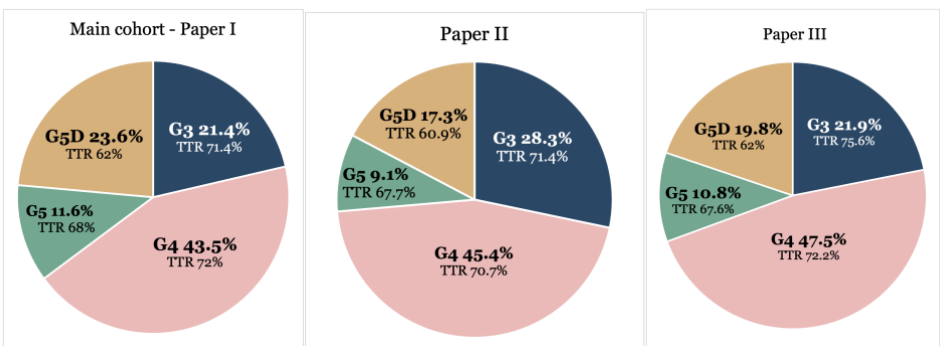

Figure 8. Proportion of patients in G3-G5D at inclusion as well as overall TTR in the different GFR categories.

At baseline, among the 12106 patients in paper I (main cohort) 13.7% was on warfarin, 55.7% had no anticoagulants and 30.6% had undefined treatment. Undefined treatment could be warfarin treatment not matching a treatment period in AuriculA or evidence of DOAC treatment. A greater proportion of men than women had warfarin treatment. Patients could switch treatments and the proportion of patients with anticoagulant treatment, warfarin and undefined,

decreased along with declining GFR. In paper II, t0 starts at a patients first warfarin treatment period from AuriculA or DOAC treatment period from PDR. Here, patients with long-term OAC treatment were excluded. At baseline, 59% of patients had warfarin and 41% DOAC (predominantly, >80%, apixaban). All patients in paper III were on warfarin, AuriculA treatment periods only, at baseline. Overall warfarin treatment quality, TTR, in the main cohort and paper III was 70% and 67% in paper II (were long-term OAC users were excluded). In all three papers TTR decreases along with declining GFR.

Table 4. Baseline characteristics main cohort (paper I)

Characteristics	**Total n=12106**	**CKD G3 n=2588**	**CKD G4 n=6090**	**CKD G5 n=2605**	**CKD G5D n=4179**	**OAC naïve n=5916**
Demographics						
Age	77.3 (71-82.7)	76.7 (71.4 - 82.0)	78.6 (72.7 - 83.5)	78.4 (71.7 - 83.8)	75 (68.2 - 80.5)	77.2 (70.1-83.1)
Female	3831 (31.6)	583 (22.4)	1990 (32.7)	874 (33.6)	1230 (29.4)	2015 (34)
Medical history						
Diabetes mellitus	5528 (45.7)	1264 (48.8)	2840 (46.6)	1202 (46.1)	2009 (48.1)	2642 (44.7)
Hypertension	10867 (89.8)	2346 (90.6)	5517 (90.6)	2416 (92.7)	3782 (90.5)	5282 (89.3)
Stroke	2513 (20.8)	485 (18.7)	1304 (21.4)	600 (23.0)	839 (20.1)	1209 (20.4)
TIA	1095 (9)	250 (9.7)	593 (9.7)	241 (9.3)	341 (8.2)	478 (8.1)
COPD	1674 (13.8)	403 (15.6)	865 (14.2)	350 (13.4)	551 (13.2)	774 (13.1)
Cancer	3521 (29.1)	727 (28.1)	1771 (29.1)	787 (30.2)	1263 (30.2)	1746 (13.2)
Congestive heart faliure	6675 (54.3)	1436 (55.5)	3569 (58.6)	1434 (55)	2197 (52.6)	2805 (47.4)
Myocardial infarction	3994 (33)	824 (31.8)	2075 (34.1)	839 (32.2)	1468 (35.1)	2031 (34.3)
Anaemia	4754 (39.3)	861 (33.3)	2322 (38.1)	1136 (43.6)	1970 (47.1)	2545 (43)
Dementia	212 (1.8)	35 (1.4)	114 (1.9)	56 (2.1)	61 (1.5)	134 (2.3)
Liver disease	474 (3.9)	115 (4.4)	211 (3.5)	84 (3.2)	200 (4.8)	271 (4.6)
Excessive alcohol use	532 (4.4)	130 (5)	241 (4)	103 (4)	206 (4.9)	309 (5.2)
History of falls	1436 (11.9)	237 (9.2)	728 (12)	340 (13.1)	551 (13.2)	778 (13.2)
Any previous major bleeding	5342 (44.1)	1074 (41.5)	2606 (42.8)	1215 (46.6)	2165 (51.8)	2648 (44.8)
Gastrointestinal bleeding	1916 (15.8)	361 (13.9)	945 (15.5)	443 (17)	825 (19.7)	1019 (17.2)
Intracranial bleeding	498 (4.1)	98 (3.8)	266 (4.4)	123 (4.7)	193 (4.6)	275 (4.6)
CHA_2DS_2-VASc	5 (4-6)	5 (4 - 6)	5 (4 - 6)	5 (4 - 6)	5 (3 - 6)	5 (3 - 6)
Treatment						
Warfarin	1656 (13.7)	444 (17.1)	1011 (16.6)	375 (14.4)	405 (9.7)	-
Undefined[b]	3707 (30.6)	1156 (44.6)	2260 (37)	800 (30.7)	943 (22.5)	-
No treatment	6743 (55.7)	990 (38.2)	2830 (46.4)	1433 (54.9)	2843 (67.8)	5916 (100)

[a] Data presented with categorical variables: count (percentage) and numerical variables: median (Q1-Q3). Note, since a patient can progress from CKD G3 to G4 to G5 to G5D, a unique patient can be present in one to all four GFR categories.

[b]Undefined consists of 18% treatment periods with DOAC.

Table 5. Baseline characteristics (paper II) for 2453 patients at the time of first treatment with either warfarin or DOAC, as well as the corresponding treatments restricted to only new treatments (no OAC within 12 months prior). Baseline characteristics for patients exclusively on correctly dosed apixaban restricted to G3-G5 is also presented. [a]

Characteristics	**Total n=2453**	**First DOAC n=1095**	**First warfarin n=1495**	**New DOAC n=463**	**New warfarin n=699**	**Correctly dosed apixaban G3-G5 n=715**
Demographics						
Age	76.7 (70.9–81.8)	77.4 (72.0 - 82.4)	76.4 (70.1 – 81.4)	78.5 (72.7 - 83.6)	76.2 (69.3 - 81.6)	79.1 (73.5 - 83.6)
Female	783 (31.9)	383 (35.0)	448 (30.0)	169 (36.5)	197 (28.2)	267 (37.3)
CKD G3	693 (28.3)	471 (43)	264 (17.7)	193 (41.7)	80 (11.4)	216 (30.2)
CKD G4	1113 (45.4)	541 (49.4)	650 (43.5)	238 (51.4)	263 (37.6)	470 (65.7)
CKD G5	222 (9.1)	37 (3.4)	195 (13)	13 (2.8)	101 (14.4)	29 (4.1)
CKD G5D	425 (17.3)	46 (4.2)	386 (25.8)	19 (4.1)	255 (36.5)	-
Medical history						
Diabetes mellitus	1180 (48.1)	525 (47.9)	724 (48.4)	209 (45.1)	362 (51.8)	345 (48.3)
Hypertension	2288 (93.3)	1023 (93.4)	1395 (93.3)	440 (95.0)	663 (94.8)	671 (93.8)
Stroke	507 (20.7)	225 (20.5)	309 (20.7)	96 (20.7)	170 (24.3)	148 (20.7)
TIA	230 (9.4)	99 (9.0)	144 (9.6)	43 (9.3)	73 (10.4)	177 (24.8)
COPD	364 (14.8)	188 (17.2)	199 (13.3)	73 (15.8)	80 (11.4)	128 (17.9)
Cancer	704 (28.7)	278 (25.4)	459 (30.7)	123 (26.6)	227 (32.5)	202 (28.3)
Congestive heart faliure	1326 (54.1)	597 (54.5)	810 (54.2)	223 (48.2)	335 (47.9)	416 (58.2)
Myocardial infarction	832 (33.9)	352 (32.1)	527 (35.2)	152 (32.8)	259 (37.1)	232 (32.4)
Anemia	911 (37.1)	423 (38.6)	545 (36.5)	184 (39.7)	263 (37.6)	287 (40.1)
Dementia	20 (0.82)	10 (0.91)	14 (0.94)	3 (0.65)	6 (0.86)	7 (0.98)
Liver disease	92 (3.8)	45 (4.1)	51 (3.4)	17 (3.7)	22 (3.1)	31 (4.3)
Excessive alcohol use	88 (3.6)	49 (4.5)	45 (3)	20 (4.3)	20 (2.9)	22 (3.1)
History of falls	289 (11.8)	146 (13.3)	164 (11.0)	66 (14.3)	91 (13.0)	103 (14.4)
Any previous major bleeding	979 (39.9)	450 (41.1)	590 (39.5)	190 (41)	296 (42.3)	307 (42.9)
Gastrointestinal bleeding	338 (13.8)	173 (15.8)	189 (12.6)	76 (16.4)	90 (12.9)	124 (17.3)
Intracranial bleeding	94 (3.8)	61 (5.6)	38 (2.5)	28 (6)	23 (3.3)	39 (5.5)
CHA_2DS_2-VASc	5 (4 - 6)	5 (4 - 6)	5 (4 - 6)	5 (4 - 6)	5 (4 - 6)	5 (4 - 6)

[a] Data presented with categorical variables: count (percentage) and numerical variables: median (Q1-Q3). Note: patients are allowed to switch treatment during follow up, subsequently first/new warfarin- and first/new DOAC treatment periods do not represent unique patients.

Table 6. Baseline characteristics (paper III) for 2379 patients when entering a new GFR category.[a]

Characteristics	CKD G3 n=521	CKD G4 n=1302	CKD G5 n=477	CKD G5D n=696
Demographics				
Age	76.7 (71.4 - 81.9)	78.4 (72.9 - 82.9)	77.8 (71.3 - 83)	74.8 (68.4 - 80.2)
Female	97 (18.6)	402 (30.9)	140 (29.3)	184 (26.4)
Medical history				
Diabetes mellitus	260 (49.9)	625 (48.0)	239 (50.1)	358 (51.4)
Hypertension	481 (92.3)	1210 (92.9)	453 (95)	652 (93.7)
Stroke	92 (17.7)	264 (20.3)	102 (21.4)	167 (24)
TIA	55 (10.6)	139 (10.7)	40 (8.4)	83 (11.9)
COPD	84 (16.1)	182 (14.0)	57 (11.9)	81 (11.6)
Cancer	141 (27.1)	390 (30.0)	152 (31.9)	231 (33.2)
Congestive heart faliure	291 (55.9)	812 (62.4)	273 (57.2)	398 (57.2)
Myocardial infarction	183 (35.1)	473 (36.3)	157 (32.9)	257 (36.9)
Anemia	152 (29.2)	445 (34.2)	180 (37.7)	306 (44.0)
Dementia	5 (0.96)	16 (1.2)	3 (0.63)	5 (0.72)
Liver disease	21 (4.0)	31 (2.4)	7 (1.5)	30 (4.3)
Excessive alcohol use	18 (3.5)	26 (2.0)	11 (2.3)	22 (3.2)
History of falls	42 (8.1)	152 (11.7)	59 (12.4)	87 (12.5)
Any previous major bleeding	216 (41.5)	528 (40.6)	219 (45.9)	357 (51.3)
Gastrointestinal bleeding	63 (12.1)	180 (13.8)	73 (15.3)	119 (17.1)
Intracranial bleeding	15 (2.9)	34 (2.6)	16 (3.4)	26 (3.7)
CHA2DS2-VASc	5 (4 - 6)	5 (4 - 6)	5 (4 - 6)	5 (4 - 6)
Warfarin treatment quality				
Total years with INR coverage	901.7	2291.2	475.7	1054.3
Count INR measurements, median (min-max)	23 (1-169)	26 (1-263)	16 (1-184)	29 (1-370)
TTR (%)[b]	75.6	72.2	67.6	62.0
Time (%) INR <2	12.9	14.6	17.1	23.5
Time (%) INR >3	11.5	13.2	15.4	14.5

[a] Data presented with categorical variables: count (percentage) and numerical variables: median (Q1-Q3). Note, since a patient can progress from CKD G3 to G4 to G5 to G5D, a unique patient can be present in one to all four GFR categories.

[b] TTR presented as % is total time in range (INR 2-3) for all patients divided by total time with INR coverage.

[c] INR count is approximate and based on the number of changes of the INR-value of an individual. If two consecutive INR-measurements are of the same value, the count will be 1, thus, the count presented is a slight underestimation of measurements (not likely to matter for the median value)

Warfarin versus no anticoagulants in AF and CKD G3-G5D (paper I)

Primary outcomes

A total of 681 ischemic strokes were found, 2.4 (95%CI 2.2-2.6)/100 patient-years, during follow up when collected from SR. Adding strokes from NPR a total of 840 ischemic strokes were found, 3.0 (2.8-3.2)/100 patient-years. Comparing warfarin and no treatment, warfarin conferred

lower unadjusted rates of ischemic stroke than no anticoagulants in all GFR categories but G5 (**Table 7**).

Table 7. Number of events, exposed time and event rates per 100pa sorted by treatment GFR category

	Warfarin			**Undefined treatment**			**No anticoagulant treatment**		
	Time	No events	Rates (95%CI)	Time	No events	Rates (95%CI)	Time	No events	Rates (95%CI)
G3	10.4	9	0.86 (0.39-1.6)	23.9	36	1.5 (1.1-2.1)	17.5	40	2.3 (1.6-3.1)
N=2588	*10.4**	*9*	*0.86 (0.40-1.6)*	*23.8*	*42*	*1.8 (1.3-2.4)*	*17.5*	*45*	*2.6 (1.9-3.4)*
G4	25.1	44	1.8 (1.3-2.4)	48.6	86	1.8 (1.4-2.2)	45.3	158	3.5 (3.0-4.1)
N=6090	*25.1**	*52*	*2.1 (1.5-2.7)*	*48.3*	*95*	*2.0 (1.6-2.4)*	*45.0*	*199*	*4.4 (3.8-5.1)*
G5	5.2	11	2.1 (1.1-3.8)	10.0	14	1.4 (0.76-2.3)	15.3	44	2.9 (2.1-3.9)
N=2605	*5.1**	*12*	*2.3 (1.2-4.1)*	10.0	*23*	*2.3 (1.5-3.5)*	*15.1*	*61*	*4.0 (3.1-5.2)*
G5D	11.6	19	1.6 (0.99-2.6)	16.7	38	2.3 (1.6-3.1)	54.5	182	3.3 (2.9-3.9)
N=4179	*11.5**	*26*	*2.3 (1.5-3.3)*	*16.6*	*51*	*3.1 (2.3-4.0)*	*53.9*	*225*	*4.2 (3.6-4.8)*

Treatment time (time) presented as years. Events presented as number of events occurred. Event rate (rate) presents events per 100 patient- years with 95% CI. Only the first type of every outcome is counted. After the occurrence of an event a patient is censored for this event but remains in the cohort for other outcomes.
*Cursive bottom row refers to strokes from SR+NPR.

There wasn't any apparent difference in major bleeding rates between warfarin and no treatment in any GFR category except G5 with higher rates of major bleeding for warfarin, 16.4 (12.9-20.6) vs 11.2 (9.5-13.1)/100 patient-years. Notably, major bleedings were much more common than ischemic strokes and bleedings were particularly common in G5-G5D for both warfarin treated- and untreated patients, bleeding rates in G5D 12.1 (10.0-14.5)/ 100 patient-years for warfarin and 10.4 (9.4-11.3)/ 100 patient-years for no treatment. Unadjusted results are presented visually with Kaplan-Meier curves in **Figure 9**.

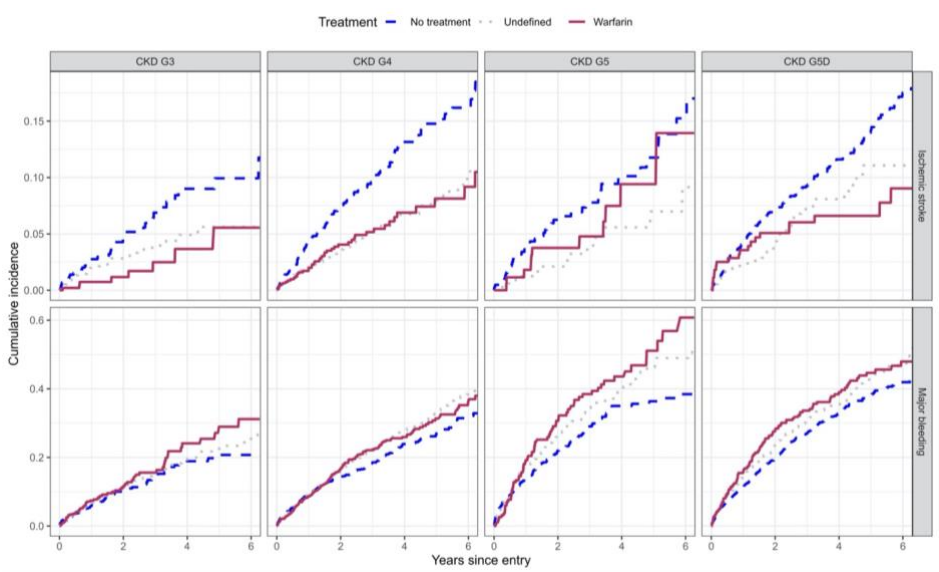

Figure 9. Cumulative incidence of ischemic stroke (from SRR) and major bleeding in the separate GFR categories.

Adjusted analysis of the whole cohort shows lower hazard of ischemic stroke for warfarin, HR 0.52 (0.41-0.67) when strokes were collected from SR, and 0.51 (95%CI 0.41-0.64) when using both SR and NPR. Undefined treatment also conferred lower risk of ischemic stroke than no treatment, 0.58 (0.49-0.68), ischemic strokes from SR+NPR. Adding the GFR category interaction, the results were consistent with lower HR of stroke on warfarin in all GFR categories but G5. **Figure 10** presents a summary of the effect of warfarin versus no OAC, here ischemic strokes are only collected from SR, but the hazard ratios if strokes are collected from SR+NPR are very similar. Adjusted analysis shows higher hazard of major bleeding for all patients on warfarin compared to no anticoagulant treatment, 1.28 (1.14-1.43). Adding the GFR-interaction, the higher hazard of bleeding isn't significant in G3 and G4, only in G5 and G5D.

Secondary outcomes
Warfarin versus no OAC lowers the hazard of all cause stroke and systemic embolism, 0.68 (0.56-0.82), a combined outcome including hemorragic stroke and peripheral embolism. HR were identical irrespective if ischemic strokes were collected from SR or SR+NPR. Warfarin increases the hazard of all types of major bleedings (intracranial bleeding 1.52 (1.12-2.08), gastrointestinal bleeding 1.18 (1.0-1.40) and other bleedings 1.32 (1.13-1.53)). The risk of all-cause mortality in the whole cohort was halved for patients on warfarin compared to no anticoagulants, 0.46 (0.42-0.50). Also, the hazard of myocardial infarction was lower during warfarin treatment in all patients, 0.74 (0.63-0.88). Hazard ratios of secondary outcomes with GFR-interaction added are found in **Figure 10**.

Sensitivity analyses
Excluding patients on dialysis (additional covariates added, including blood pressure, BMI, S/P- albumin and B-hemoglobin) the results remained robust. Warfarin conferred lower risk of ischemic stroke with HR 0.50 (0.38-0.67) when strokes were collected from SR and 0.55 (0.40-0.75) when strokes were collected from SR+NPR. Furthermore, warfarin was associated with higher hazard of major bleeding, 1.36 (1.17-1.58). Adjusted analysis of incident warfarin treatment versus no anticoagulants also showed lower risk of stroke (collected from SR+NPR) but higher risk of bleeding in patients with G3-G5D, 0.37 (0.21-0.65) and 1.43 (1.16-1.77). **Figure 11** shows results of adjusted analysis with the GFR-interaction added. Also, the hazard of death was significantly lower for warfarin in all OAC naïve patients, 0.54 (0.46-0.63).

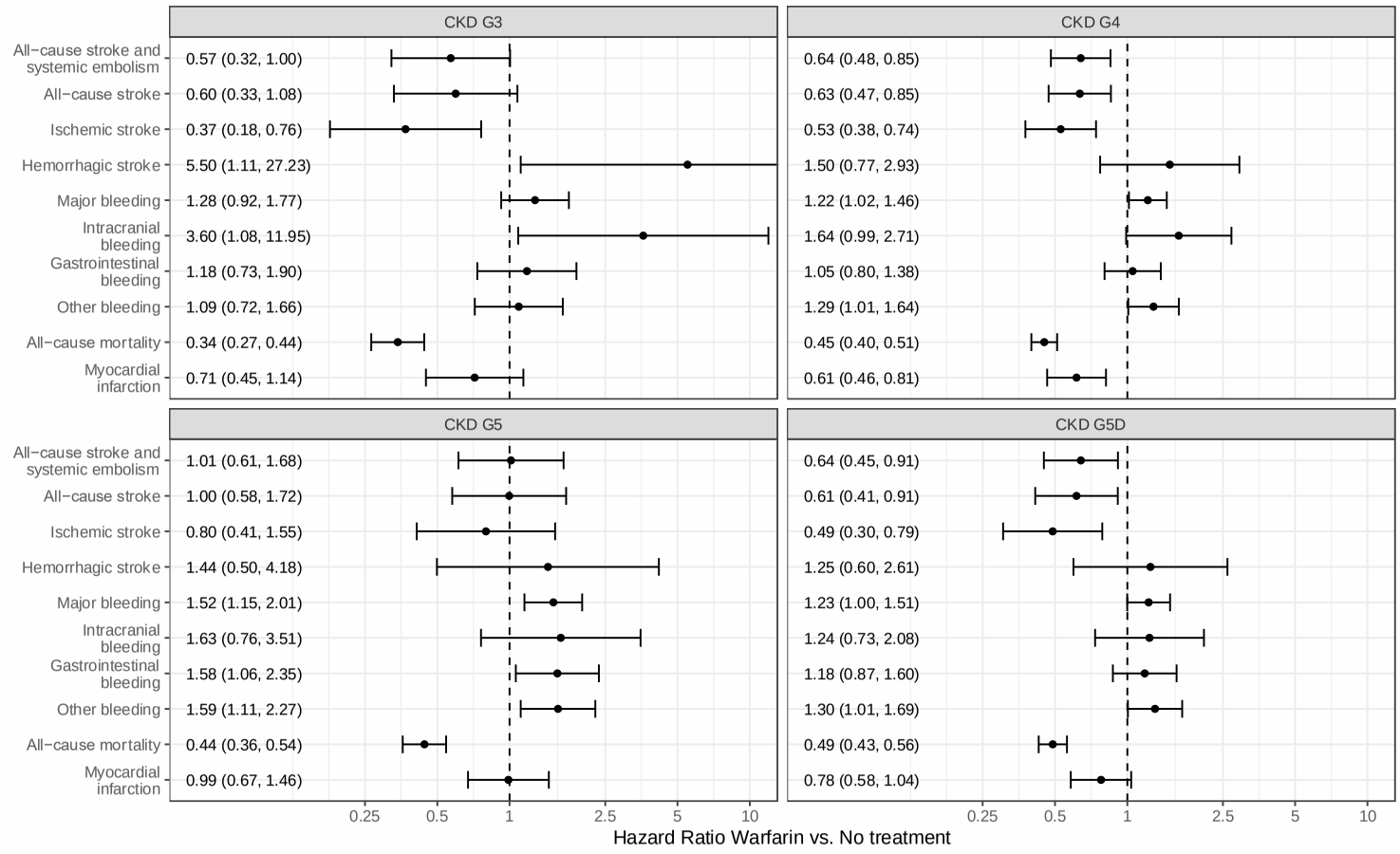

Figure 10. Summary of the effect of warfarin versus no OAC treatment in G3-G5D presented with HR (95%CI). Ischemic strokes are only collected from SR.

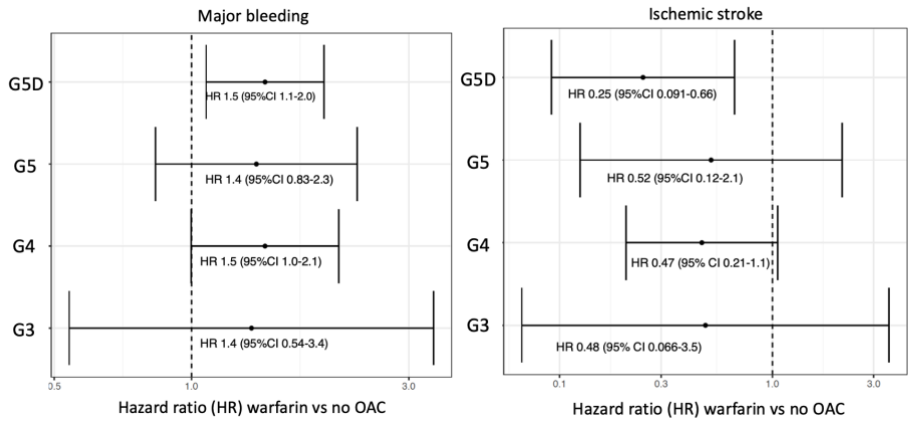

Figure 11. Effect of incident warfarin versus no OAC treatment in OAC naïve patients in G3-G5D presented with HR (95%CI). Ischemic strokes were collected from SR+NPR.

DOAC versus warfarin in AF and CKD G3-G5D (paper II)

Primary and secondary outcomes

DOAC and warfarin (all patients considered) conferred similar rates of ischemic stroke and death, but patients on DOAC had lower bleeding rates, 6.3 (5.0-7.8) vs 9.7 (8.6-10.9)/100 patient-years, (Kaplan-Meier curves presented in **Figure 12**). Similar to findings in paper I, major bleedings were more common than ischemic stroke, with 10 times higher bleeding rate than stroke rate for DOAC in G5/G5D, 17.4 (8.9-31.3) bleedings vs 1.7 (0.1-8.5) ischemic strokes/100 patient-years.

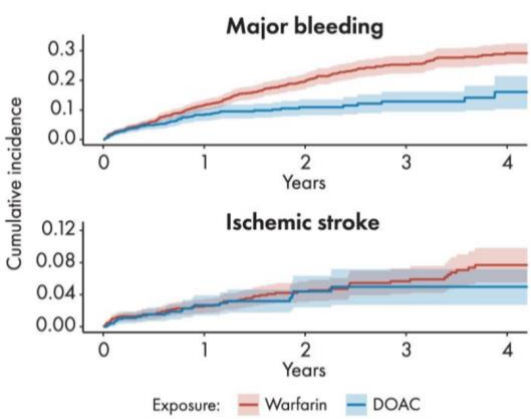

Figure 12. Kaplan–Meier curves for major bleeding and stroke, comparing treatment periods of warfarin (red) and DOAC (blue). Graphs presented with years since t0 (up to 4 years) on the x-axis and cumulative incidence on the y-axis.

Adjusted analysis of DOAC compared to warfarin conferred lower hazard of major bleeding, HR 0.71 (95%CI 0.53-0.96), in all patients, a result

that seems mainly driven by patients in G4 (GFR category interaction added), presented in **Figure 13**. The hazard of stroke did not differ between the treatments. The hazard of all-cause mortality was slightly, but significantly, higher in patients on DOAC compared to warfarin, 1.24 (1.01-1.53), which seems mainly driven by patients in G4 when GFR-interactions added. This result was not reflected by more fatal bleedings on DOAC; 1 patient on DOAC compared to 13 patients on warfarin died within 7 days of a major bleeding.

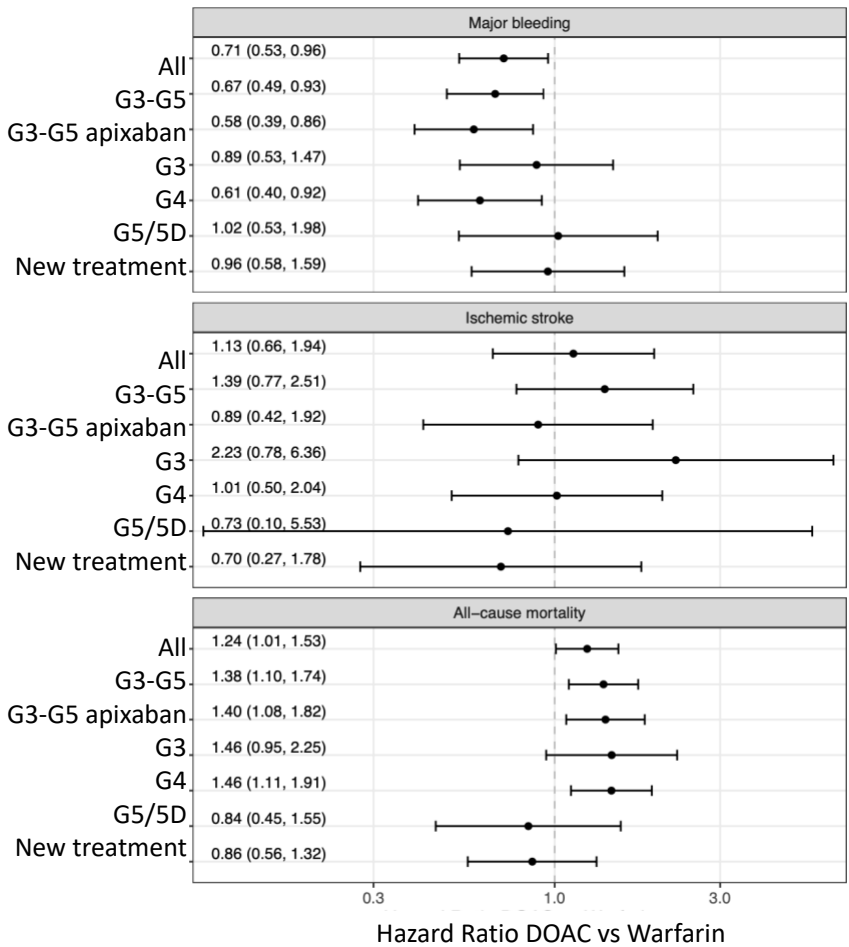

Figure 13. Summary of the effect of DOAC versus warfarin treatment in G3-G5D presented with HR (95%CI). All patients, G3-G5, G3-5 correctly dosed apixaban using model 1, G3, G4 and G5/5D using model 2.

Sensitivity analyses

The results from main analysis remained robust also when excluding G5D, with lower hazard of major bleeding, 0.67 (0.49-0.93), higher hazard of death, 1.38 (1.10-1.74) and no significant difference in hazard of ischemic stroke (**Figure 13**). Repeating the analysis but comparing

only correctly dosed apixaban and warfarin in G3-G5 showed lower hazard of major bleeding, 0.58 (0.39-0.86), higher hazard of death, 1.40 (1.08-1.82) and no difference in stroke risk. New DOAC treatment compared to new warfarin treatment however did not show any difference in stroke- and bleeding risk or death.

Importance of warfarin treatment quality (paper III)

Figure 14 shows how iTTR is distributed in the GFR categories over time. Along with decreasing eGFR, TTR (and iTTR) also decreased and the proportion of subtherapeutic iTTR increased in relation to supratherapeutic iTTR, when not in range (**Table 6**). 10 percentage points (pp) increase in iTTR lowers the hazard of major bleeding, ischemic stroke and death in all patients (0.91 (0.87–0.94), 0.92 (0.85–0.995) and 0.88 (0.85–0.90)), presented in **Figure 15**. However, in subgroup analysis of G3-G5 and G5D separately, the effect on stroke is not significant. Comparing outcomes in relation to iTTR<and $\geq$ 70% in an adjusted analysis showed iTTR $\geq$70% conferred lower risk of major bleeding in all patients, 0.63 (0.51-0.77), in G3-G5, 0.62 (0.48-0.81), and the same, however non-significant tendency was seen in G5D, 0.7 (0.46-1.06). There was no difference in the hazard of ischemic stroke comparing iTTR above or below 70% in all patients, G3-G5 and G5D. iTTR $\geq$70% was associated with lower hazard of death in all patients, 0.51 (0.43-0.61), G3-G5, 0.49 (0.40-0.61), and G5D, 0.61 (0.44-0.83).

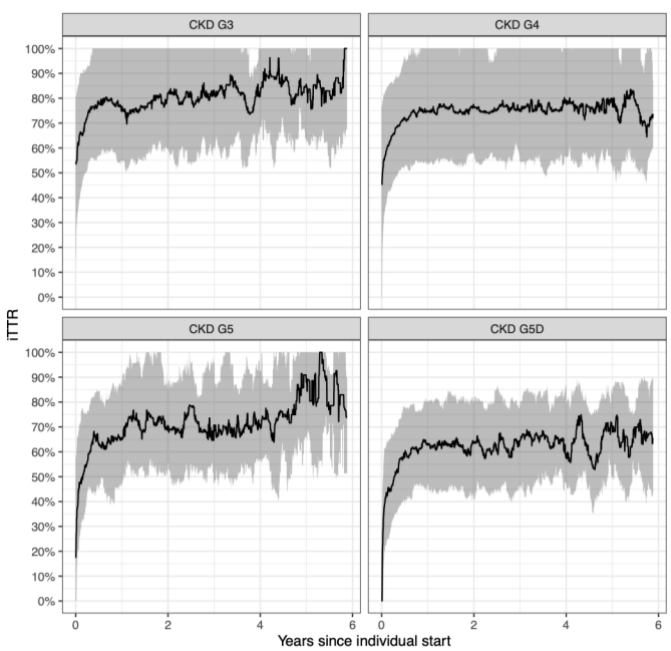

Figure 14. iTTR (%) quartiles (black line=median, Q2) Q1-Q3 is represented by the grey area.

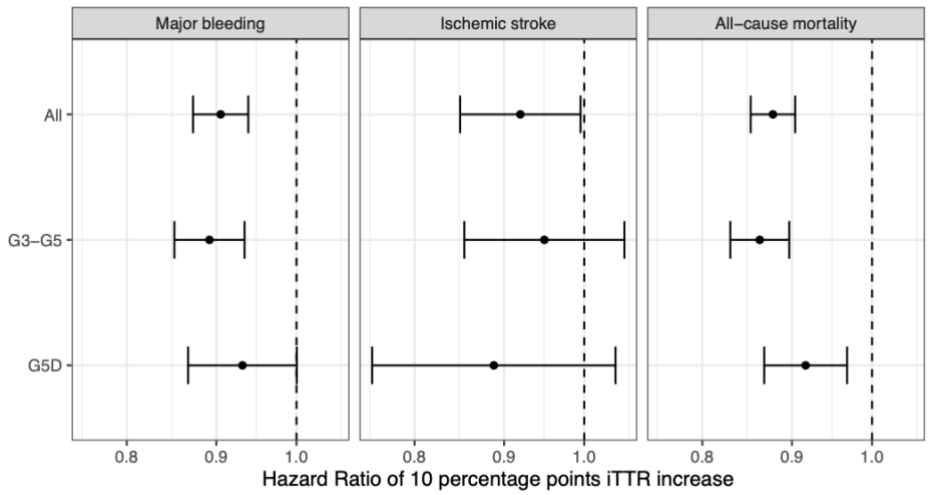

Figure 15. Adjusted model for effect of 10 percentage points increase in iTTR on major bleeding, ischemic stroke and all-cause mortality with respect to GFR category in 2379 CKD G3-G5D warfarin treated patients with NVAF.

Paper IV – Prophylactic anticoagulants in nephrotic syndrome

Cohort description

In total 95 patients were included. Patients in PAC group (n=40) and no PAC group (n=55) were comparable in age, sex, and smoking habits. Hypertension, diabetes mellitus, previous kidney disease and anaemia were more common in no PAC group. Median S/P-albumin was lower in PAC group (17 vs 26 g/L) and eGFR was higher in PAC group (69 vs 32 ml/min/1.73m^2). Diagnose causing NS was mainly minimal change disease and membranous nephropathy in PAC group, in no PAC group diabetic nephropathy was most common (**Table 8**). Total follow up time was 36877 days, median follow up 365 days.

Choice and regime of anticoagulants
In PAC group, 15 patients had low dose (≤5000IU daily) and 10 had high dose (>5000IU daily) dalteparin as their most intense anticoagulant treatment. For PAC patients receiving OAC, 12 received warfarin as their most intense therapy (often with dalteparin bridging) and 3 received DOAC (type of DOAC not specified).

Table 8. Underlying diagnose from kidney biopsies

	PAC n=40	**No PAC n=55**
Minimal change disease (MCD)	15 (37.5)	9 (16.4)
Membranous nephropathy (MN)	14 (35.0)	2 (3.6)
Focal segmental glomerulosclerosis (FSGS)	2 (5.0)	4 (7.3)
Membranoproliferative glomerulonephritis	0	4 (7.3)
IgA nephropathy	4 (10.0)	5 (9.1)
Diabetic nephropathy	1 (2.5)	17 (30.9)
Hypertensive nephrosclerosis	0	3 (5.5)
Other	4 (10.0)	11 (20.0)

Results are presented as n (%).

Outcomes

Venous thromboembolism and bleedings

A total of 7 VTE events occurred, all within the first year after diagnosis yielding an annual incidence of 7.4%, with no significant differences between PAC- and no PAC group (**Figure 16**). Mean time to VTE was 151 days (minimum 8, maximum 283). Among the 4 VTE in the PAC group 2 pulmonary embolisms (PE) occurred while ongoing PAC treatment (on PAC); the first diagnosed after 2 days of high dose dalteparin, the second after 13 days of low dose dalteparin. The remaining two VTE in PAC group occurred after a 3–4 days interruption of PAC (off PAC) due to kidney biopsy. Of patients with MN and MCD, 18.8% and 8,3% respectively had an VTE, compared to 3.6% in other diagnoses (1 patient with diabetic nephropathy, 1 patient with "other" diagnosis), however the difference in VTE occurrence between diagnoses was not statistically significant.

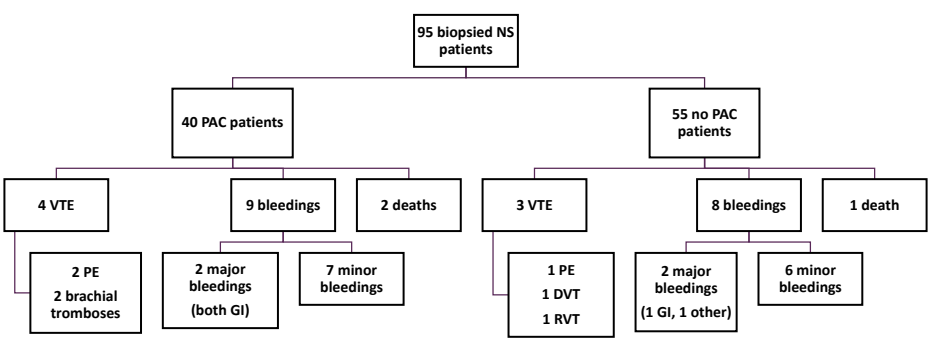

Figure 16. Number of outcomes in different treatment groups.

There was no significant difference in the occurrence of bleeding in PAC and no PAC group. Notably, only one patient in the PAC group was on PAC treatment (warfarin, INR is missing) at the occurrence of a major bleeding. Three of four patients with major bleeding had an eGFR of ≤30 ml/min/1.73m^2 at the time of bleeding (eGFR was missing for the 4th patient with bleeding). The majority of minor bleedings were subcapsular bleedings after kidney biopsy, none caused hemodynamic instability. Four minor bleedings occurred on PAC and 3 off PAC. Seven arterial thromboses, 2 in the PAC group and 5 in the no PAC group, were also noticed, including ischemic stroke and myocardial infarction. Rate of outcomes/100 patient-years depending on S/P-albumin interval and the ratio between the albumin interval are presented in **Table 9**.

Excluding patients with diabetic nephropathy in a sensitivity analysis created more similar groups but still differing in S/P-albumin and occurrence of previous anemia (lower albumin and less anemia in PAC group), there was still no difference in outcome frequency between the groups.

Table 9. Rate of outcomes in two S/P-albumin intervals

		S/P-Albumin <20g/L	**S/P-Albumin ≥20g/L**	**Incidence rate ratio (IRR)**
VTE	**total**	69.7 (22.1–168.1)	3.2 (0.8–8.7)	21.7 (4.5–116.5)
	on PAC	51.8 (8.7–171.1)	-	-
	off PAC	106.5 (17.9–352.0)	3.9 (0.9–9.7)	29.8 (3.5–200.2)
Bleeding, total	**total**	87.1 (31.9–193.1)	13.9 (7.7–23.2)	5.0 (1.4–14.7)
	on PAC	25.9 (1.3–127.7)	31.0 (7.9–84.3)	0.8 (0.03–7.8)
	off PAC	159.8 (40.7–434.9)	11.9 (6.1–21.3)	13.4 (29.7–462.2)
Major bleeding	**total**	17.4 (0.9–85.9)	3.2 (0.8–8.7)	5.4 (0.2–51.0)
	on PAC	-	10.3 (0.5–50.9)	-
	off PAC	53.3 (2.7–262.7)	2.4 (0.4–7.9)	22.3 (0.8–293.6)
Minor bleeding	**total**	156.8 (76.5–297.7)	10.7 (5.4–19.0)	4.9 (1.1–16.9)
	on PAC	25.9 (1.3–127.7)	20.6 (3.5–68.2)	1.3 (0.04–16.5)
	off PAC	106.5 (17.9–352)	9.5 (4.4–18.1)	11.2 (1.6–48.3)

Rate of outcomes/100 patient-years depending on S/P-albumin < and ≥20g/L . Separate rates were calculated for time in total, time on PAC and time off PAC. Data presented as event rate per 100 patient-years (95%CI) and incidence rate ratio (95%CI).

Discussion

OAC in AF and CKD G3-G5D

Warfarin versus no anticoagulants

The main finding presented in paper I is that well managed warfarin treatment (TTR 70%) in a Swedish cohort with G3-G5D is associated with lower risk of ischemic stroke but higher risk of major bleeding. Similar results in the sensitivity analyses implies robustness of the results. Warfarin-treatment for stroke prevention in G3-G4 is established. Although no RCTs have been designed for proving its efficacy in G4, several observational studies indicate its applicability (85, 96, 147, 168, 169). In G5-G5D however, the stroke prophylactic role of warfarin is less clear. Warfarin is the only approved OAC in G5/G5D in Sweden and Europe, but available observational data show heterogenous results on stroke prevention and available meta-analyses do not show a clear benefit (147, 151, 170). Notably, almost all previous studies present either low TTR (or no TTR) which reduces their credibility. The Scandinavian countries are renowned for high warfarin treatment quality. It might not be a coincidence that the observational studies from Sweden and Denmark (including ours) also show stroke prophylactic effect in CKD cohorts, even in G5D (142, 143, 168). It is plausible that if high TTR is achievable, warfarin is a valid option for stroke prevention also in G5D. Subgroup analysis of G5 in paper I did not show a clear benefit for warfarin regarding stroke prophylaxis. This could be due to the assumed heterogenous composition of G5, with patients not yet started KRT as well as more frail patients not suitable for KRT. The potential stroke reducing effect of warfarin in G5 might be diminished by the high baseline risk of stroke in this group and by difficulties keeping these patients in INR range.

The higher risk of bleeding in warfarin treated patients with CKD seems mainly driven by patients in G5-G5D. The same pattern was found in the meta-analysis by Dahal, where the increased risk of bleeding only was seen in kidney failure (147). Studies mainly including G3-G4 do not show increased risk of bleeding on warfarin (169). The increased risk of bleeding on warfarin in G5/G5D seems undebatable and is repeatedly shown (151, 170). Importantly, the bleeding risk is increased from an already high level.

Mortality is more than halved for patients on warfarin, consistent in all subgroup analyses. The lower stroke risk could contribute to this but

there could also be other positive effects on cardiovascular disease. However, it is reasonable to think that the group of warfarin treated patients is affected by indication bias and prescription of warfarin to healthier, less frail patients who are less likely to die.

High quality warfarin treatment seems safer in early CKD stages, and a well-functioning warfarin treatment mustn't necessarily be replaced by DOAC. However, warfarin has to be prescribed with extreme caution in G5-G5D, and the bleeding risk must be assessed carefully. Furthermore, attention should be given to a patient's risk of vascular calcification and calciphylaxis before deciding on OAC. If high TTR isn't achievable or a patient has several risk factors for calciphylaxis, other treatment options should be considered such as no treatment, recruiting to a study or DOAC off label.

DOAC versus warfarin

The main finding presented in paper II is that DOAC, mainly apixaban, compared to well managed warfarin (TTR 67%), is associated with lower risk of major bleeding but no difference in the risk of ischemic stroke. The similar stroke preventive effect of DOAC and warfarin has also been shown in several other studies including mainly G4-G5D (116, 153, 171). However, the VALKYRIE-trial wasn't powered to assess stroke risk. A meta-analysis by Su et al. including G3-G5 saw a slight benefit of DOAC, however they mainly included G3-G4 (including data from the pivotal RCTs) and few patients with G5.

The favorable bleeding profile of DOAC compared to warfarin in CKD was also seen previously (116, 153, 171, 172). Adding GFR interactions in paper II, the lower hazard of bleeding is mainly driven by patients in G4, which was the largest group. In G3 and G5/G5D, no significant difference was seen. One could speculate that a warfarin TTR of 71.4% in G3 might diminish the favorable bleeding profile of DOAC seen in the pivotal trials, where TTR was lower. In G5/G5D, the high baseline risk of bleeding might make it difficult to perceive differences in bleeding between the treatments. The VALKYRIE-trial did show a benefit for bleedings with Rivaroxaban. However, the TTR in their warfarin comparison group was only 48% which probably entails bleeding disadvantages to warfarin. A recent meta-analysis including patients on hemodialysis showed no difference in bleedings between DOAC and VKA (173). Studies comparing DOAC and VKA are difficult to compare since there are so few and differ in TTR and the type of DOAC.

Paper II presents a small, but significant, increased risk of all-cause mortality in DOAC treated patients. This was not reflected by more fatal

bleedings on DOAC which implies that the association isn't necessarily causal. More likely, the suggested higher risk of death is a result of the many biases and confounders that hampers an observational study. However, it does call for caution, since this signal also was seen in RENAL-AF with numerically more deaths on apixaban, although that study was underpowered and did not go further with adjusted analyses (117).

The DOAC group is heterogenous including all DOACs and all doses, but the results remain consistent when including only correctly dosed apixaban. However, with inclusion of only incident treatments the favorable effect of DOAC disappears. This group is too small do draw further conclusions. DOAC, especially apixaban, therefore seems at least comparable to well managed warfarin. DOAC is a compelling alternative to warfarin due to its simplicity and lack of associations with vascular calcification and calciphylaxis.

The importance of warfarin treatment quality

We concluded in Paper III that increasing iTTR is associated with lower risk of major bleeding, ischemic stroke and all-cause mortality in all patients. This reiterates the results of similar studies implemented in a general population as well as in CKD-cohorts that mainly included G3-G4. In subgroup analysis, the importance of iTTR isn't as obvious. The wider confidence intervals, in especially G5D, are possibly a result of small groups. Even though we couldn't prove a reliable effect of iTTR on outcomes in G5D, high iTTR is probably even more important in these patients than in patients with earlier stages of CKD, due to the high risk of bleeding. The lack of difference in stroke prevention between iTTR> and<70% might be due to few stroke events and that the group with the highest risk of stroke (G5/G5D) could often not reach iTTR of 70%. Maybe the cut off should have been set lower to reveal the effect? Another explanation could be that many ischemic strokes, although AF is present, aren't thromboembolic in CKD. The attributable stroke risk of AF in CKD, as mentioned previously, is probably lower than in a general population.

Is OAC at all warranted in AF and G5/G5D?

Not all patients with NVAF and G5/G5D should have OAC. On population level, there isn't sufficient evidence for treating patients in G5/G5D with OAC due to the high risk of bleeding and divergent data on efficacy. Nevertheless, OACs are prescribed worldwide on this indication, since we want to protect our patients from disability and death. Our study comparing high quality warfarin with no OAC indicates that OAC

might provide stroke prevention even in G5D. However, Su et al. concludes that there are no benefits with OAC in G5D, only significantly increased bleeding risk (172). Mavrakanas et al. compared apixaban versus no OAC and reported no difference in the primary outcome of stroke, systemic embolism or TIA but significantly higher risk of fatal- or intracranial bleeding (174).

Faced with the choice between ischemic stroke and major bleeding there is no obvious right path. A stroke can be everything from minor, with no evident residual disability, to a large stroke that is instantly or eventually fatal. We did not include any measurements grading stroke symptoms or quality of life measurements. This would have enriched the results, even though recovery from stroke and quality of life might be highly dependent on the patient's comorbidities and physical condition and it might not always reflect the severity of the event of interest. We do however know that the strokes occurring as presented in paper I-III were few, fewer than in many other studies (142, 153). This might be due to missing strokes, for example fatal events that never makes it in time to hospital, and selection bias. The low stroke rates could also be due to improvements in primary prophylaxis. Data from the National Board of Health and Welfare show that in Sweden the stroke incidence in the general population has been reduced by 50% during the 21st century, supporting the latter theory (175).

The bleeding rates, especially in G5/G5D are up to 10 times higher than the stroke rates described in paper I-III. Scrutinizing different types of bleedings presented in paper I, there is a particularly high risk of GI- and other bleedings. Intracranial bleedings have just about the same incidence rate as ischemic stroke in warfarin treated patients. A major bleeding can be everything from a large hemorrhagic stroke or a life-threatening gastrointestinal bleeding, to a minor hemorragic stroke with no or little disability or a small treatable GI-ulcer. However, even a non-life-threatening major bleeding is often a major issue since it paradoxically increases the risk of thrombosis. Both by the subsequent interruption of OAC, and by the activation of coagulation that will start inevitably. Therefore, bleeding should always be avoided.

If it is generally true that OAC leads to 10 times higher risk of bleeding than stroke, this is unacceptable. However, we don't know whether the same patients are at risk for both stroke and bleeding. Also, the bleeding risk is also very high in G5/G5D in patients with no OAC and OAC might only be responsible for a minority of the major bleedings. The real challenge is to find patients who are at high risk of stroke, and low risk of bleeding. This can be accomplished with RCTs comparing OAC and no

treatment, scoring systems validated in CKD and more knowledge about uremic platelet dysfunction and how this could be practiced in clinic. In the meantime, OAC should not be routinely prescribed in G5/G5D, patients should instead, if possible, be enrolled in a study. If a study isn't suitable or available, bleeding- and stroke risk must be assessed to the best ability of the physician and an individual decision, involving the patient's own wishes, is preferable. Still, it's reasonable to offer OAC to patients who have had a thromboembolic stroke or TIA and have a low risk of bleeding.

Gender disparities in anticoagulant prescription in AF

It was highlighted in paper I that women less often than men were prescribed warfarin. However, in paper II, we saw that the female proportion of DOAC users (first DOAC) was larger than the proportion of female warfarin users (first warfarin). If women overall were prescribed less OAC in our cohort is yet to be examined. The larger female proportion of the DOAC users compared to the traditional substance warfarin might suggest that the prescription of OAC to women is increasing. If this is true, it is an important step forward. Female sex is a risk factor for stroke, and women do not seem to have higher bleeding risk than men, but have been underrepresented both in the pivotal DOAC trials as well as in OAC prescription (176).

Nephrotic syndrome and the risk of thrombosis

As presented in Paper IV, 7.4% of patients with NS experienced a VTE, all within the first year of follow up. A majority of the VTE events occurred in MN and MCD. Our findings are in line with previous research. Clinically apparent VTE was reported in 7.2% of patients with MN in one of the largest retrospective studies published.
In studies where radiological screening methods were used a larger number VTE were detected, where a majority were asymptomatic (58, 177, 178). Mahmoodi et al. reported a VTE incidence of 9.85% the first 6 months in a retrospective study including patients with MN, MCD, FSGS, MPGN and diabetic nephropathy (56). They saw the highest incidence rate of VTE in MN and lowest in diabetic nephropathy. Waldman et al. found clinically apparent VTE in 4% of patients with MCD, while Fenton et al. reported 12% in the same disease (179, 180). A study comparing disease specific risk for VTE in glomerular diseases (n=1313) showed a 10.8 times higher risk of VTE in patients with MN and a 5.9 times higher risk in FSGS compared to IgA nephropathy (181). Although s-albumin was adjusted for, this study wasn't specifically investigating nephrotic patients. To conclude, the elevated risk of

thrombosis in NS is most evident in MN with at least 7% experiencing clinically apparent VTE. The VTE risk seems less pronounced in other primary and in secondary causes of NS.

In our study, there was no significant difference in VTE occurrence between the PAC group (10% experienced VTE) and no PAC group (7% VTE). Conclusions from this result are difficult to draw, since the groups differed at baseline regarding important risk factors for VTE such as subtype of NS and baseline S/P-albumin. Still, some aspects regarding the VTE risk in this study should be highlighted. First, there were strikingly many patients affected by VTE in the group where prophylaxis was given. Patients in the PAC group seem very prone to VTE, and they indeed did have a higher assumed baseline risk of VTE as membranous nephropathy was overrepresented in that group (14 vs 2) and they also had significantly lower s-albumin at baseline. It is likely that this group would have experienced even higher rate of VTE events without PAC. Second, patients developed VTE during a very brief pause of PAC. At kidney biopsy PAC has to be withdrawn, yet other precautions can be taken for patients with high risk of thrombosis. Suggestions are wearing compression socks, staying well hydrated before the biopsy. When bedrest after kidney biopsy is completed the patient should avoid immobilization, Also restricted use of iv lines to minimize the risk of iatrogenic thrombosis could be considered (182).

Minor and major bleedings occurred in 18% of patients, 4% of patients experienced a major bleeding. Major bleedings were as common in PAC group as in no-PAC group and only one major bleeding occurred on-treatment. Thus, there were other factors involved in the other bleedings. Low GFR is probably the most important risk factor, ¾ bleedings occurred in patients with eGFR<30ml/min/1.73m^2,and eGFR is missing for the 4th patient with bleeding. The bleeding risk in patients receiving PAC in NS is not very well described previously. Kelddal et al. reported 11% bleedings (4.5% major bleedings) in a PAC-regime similar to the one in paper IV.

Besides presenting the overall high risk of VTE and bleeding in NS, paper IV also highlights the risk of patient-time with severe hypoalbuminemia. S/P-albumin<20g/L confers significantly higher rates of VTE as compared to S/P-albumin>20g/L, irrespective of treatment. The method used to estimate a daily S/P-albumin and how this is associated with the risk of thrombosis strengthens the previously reported association between thrombosis and hypoalbuminemia (58). Time with severe hypoalbuminemia also seems associated with higher risk of bleeding. Since we didn't adjust for confounders, we don't know

whether the effect of hypoalbuminemia on bleeding is a true effect. There is a derangement in both pro- and anticoagulant factors in NS which could be lead to a paradox state, with risk of both bleeding and thrombosis. Hypoalbuminemia is indeed a vulnerable state. Our findings indicate that this also needs to be taken into the bleeding risk calculation when deciding on PAC.

Are prophylactic anticoagulants in NS warranted?

There is no clear evidence how to handle PAC in NS. Due to lack of RCTs comparing PAC and no PAC, as well as different PAC regimes, we can only form our decisions on guidelines that are based on observational data and eminence opinion. The most convincing evidence for using PAC is within the first 6 months after diagnosing MN, where at least 7% of patients experience a VTE event. The least convincing evidence for PAC is in secondary causes of NS, due to for example diabetic nephropathy, where a distinct increase in VTE risk is not well established. For NS in primary glomerular disease, MCD, FSGS and MPGN there seems to be an increased VTE risk, but evidence is lacking if benefit with PAC upweights the risks.

A recent meta-analysis compared the incidence of VTE in studies where the majority of patients had received PAC (2-3% VTE) with patients not receiving PAC (10.6% VTE) (183). The authors suggest a potential benefit of PAC in NS, however due to the heterogenicity of included patients and treatments in the studies, this needs to be proven in RCTs. This study also highlighted the non-negligible risk of bleeding in PAC use but wasn't able to show a significantly increased risk of major bleedings between PAC treated and untreated patients (Odds ratio 2.08 (95%CI 0.41-10.45).

The KDIGO guidelines on glomerular diseases suggest to use a flow chart when deciding on PAC in NS (66). If s-albumin is <20g/L with BCP assay (<25g/L with BCG), the risk of VTE is high and the benefit-risk-ratio of thrombosis and bleeding should be assessed with GN-tools (https://www.med.unc.edu/gntools/index.html). The GN-tool is however intended only for use in membranous nephropathy and is based on Markov modelling of an observational cohort by Lionaki (58, 184). Therefore, extrapolating the use of this tool to other primary (or secondary) causes of NS should be done with caution, since these patients seem to have lower baseline risk of VTE, but the bleeding risk might be similar. Moreover, KDIGO identifies risk factors associated with high risk of VTE such as membranous nephropathy, proteinuria>10g/day, BMI>35kg/m^2, genetic predisposition for VTE, Heart failure New York Heart Association class III-IV, recent orthopedic

or abdominal surgery and prolonged immobilization. There are many more risk factors for VTE, for example active malignancy, smoking, previous VTE that has to be considered. Lin et al. proposed an alternative algorithm for decision aid, recognizing the difference between MN and other primary causes of NS (185). As bleeding assessment, they used HAS-BLED instead of the ATRIA bleeding score used in GN-tools, due to better performance in predicting bleeding (186). The decision aid does not state what albumin assay is used, which is a drawback. None of these algorithms are based on high quality evidence and even in MN, they should be used with caution, carefully weighting the bleeding and the VTE risk.

Should diabetic nephropathy with heavy albuminuria and hypoalbuminemia also be considered at high VTE-risk? Mahmoodi et al. found 1 clinically apparent VTE in 32 diabetic patients with lower annual incidence (0.58/year) than in other glomerular diseases. Our study showed only 1 VTE in 18 patients with diabetic nephropathy. Although the VTE risk might be higher in diabetic NS than in a general population it might not be high enough to justify PAC. There is no clear evidence how to handle secondary NS and the GN-tool should probably not be used here. Instead, secondary causes of NS should be considered as risk factors for VTE and be weighted together with other risk factors, as in all patients. Patients with NS where PAC is abstained can be informed of the potentially higher thrombotic risk, and might be suggested to use compression socks, even though the evidence behind this is poor (182).

Due to the lack of both high quality RCTs as well as high quality observational data, the evidence for how to prescribe PAC is low. KDIGO recommends warfarin (INR range 2-3) or heparins. Warfarin does seem reasonable in MN with severe hypoalbuminemia or other primary causes of NS with additional risk factors for VTE. However, if bleeding risk is high, a plausible alternative is low dose LMWH or abstained treatment. Important to remember is that PAC should be withdrawn when s-albumin increases>20g/L (BCP), if no other risk factors for VTE are present, and can be reevaluated after 6 months when the VTE risk is often reduced.

Is DOAC an option for VTE prophylaxis or treatment in NS? A small RCT (phase 1a, n=22) comparing apixaban pharmacokinetics in NS compared to healthy controls showed higher free concentration and $AUC_{0\text{-}24}$ of apixaban and slower free apixaban clearance in NS, however not statistically significant (187). A mechanism for slower clearance could be the disproportionate greater protein-bound clearance in heavy albuminuria. Due to study size, no further conclusions should be drawn.

This study however highlights that DOAC pharmacokinetics in NS are altered, and DOAC cannot be recommended on this indication yet.

KDIGO guidelines furthermore suggest aspirin in NS with S/P-albumin 20-30g/L (BCP assay) in patients with risk factors for arterial thromboembolism (ATE), using the Framingham risk score (66, 188). This recommendation is based on a suggestion in a commentary article by Hofstra, but it raises some concerns (189). First, aspirin should not be used as ATE-prophylaxis, but the use of Framingham risk score suggests that it is arterial cardiovascular events in general (such as myocardial infarction) rather than ATE from atrial fibrillation that the authors are referring to (75). Second, aspirin as primary prophylaxis of cardiovascular disease has not yet been proven effective, in NS, in CKD or in the general population, although we do await results of the ATTACK (aspirin to target arterial events in chronic kidney disease) trial NCT03796156 (190). No studies have compared aspirin with no PAC or aspirin with LMWH or warfarin. A recent Chinese RCT compared indobufen, a reversible platelet cyclooxygenase inhibitor, to warfarin in NS(67). It showed similar effects on VTE prevention but fewer minor bleeding events with indobufen. This study has several methodological concerns; high risk of bleeding was not an exclusion criterion and there are no comorbidity data presented or adjusted for in analysis; patients could have had different baseline risk of bleeding (and thrombosis), potentially affecting the outcome. Not all had a histopathological diagnosis and the distribution of subtypes of NS between the groups were uneven, probably also affecting baseline risk of thrombosis. Follow up was only 12 weeks and patients on warfarin had mean INR of approximately 1.5-1.6, which indicates that patients had suboptimal warfarin treatment. Before starting using aspirin or other antiplatelet agents widely as primary prophylaxis in NS, a large RCT needs to confirm it's benefit, and that the benefit-risk ratio is sufficient. In my opinion, this suggestion should be toned down in KDIGO guidelines.

Limitations

Retrospective design

All papers I-IV present observational studies, a study design that by its retrospective nature entails numerous inevitable bias and confounders.

The design of the studies presented in paper I-III is very similar, with a retrospective register design. The included registers and the chosen variables have high quality and coverage. Problems with this design is that no register has full coverage. For example, SRR has almost full

coverage of all patients on dialysis in Sweden, but many patients with CKD G3-G5 are not registered; due to a clinic not registering for example G3, or that the patient isn't yet referred to a nephrology outpatient clinic. The not referred patients are often older, either with a stable disease in no need of specialist care or a progressive disease but where KRT is decided unsuitable, and the intended path is conservative uremic care. Also, many patients with AF might be missing, this can be due to physicians not registering the ICD code in the medical records, or that the AF is undiagnosed, perhaps due to asymptomatic AF. These patients will not be included even though they might have high risk of stroke, and this might be another reason why the stroke rate was unexpectedly low.

Originally, study I-III was designed to include only strokes from the Swedish stroke registry. The unexpectedly low stroke rates made us widen the search for ischemic strokes also from NPR. Indeed, 159 more strokes were found. The stroke diagnosis from NPR is not as validated as the one from the stroke register. This is also the reason why we did not focus on the outcome all-cause stroke and systemic embolism since diagnoses other than stroke would be collected from NPR.
Register design creates selection bias and decreases the external validity of the study. The results should only be applied on patients in specialized nephrology care in Sweden and used with caution in other settings. The solution to dealing with many biases and confounders is of course an RCT. This is however expensive and time consuming and would not have been feasible for this type of project. Importantly, RCTs also come with selection bias; we often do not include the most frail patients, or patients with for example dementia. Therefore, a register study including all patients suitable is an important contributor to the puzzle.

The studies in papers I-III have their t0 when both eGFR<60ml/min/1.73m^2 and the diagnosis atrial fibrillation are established and thus the AF diagnosis could be both prevalent and incident. The most correct way to design the studies would have been to include only incident atrial fibrillation in patients with G3-G5D. However, this would not have been possible with this study design since the NPR does not include diagnoses from the primary care. A patient could have had an AF diagnosis (or undiagnosed AF) for many years before it is registered in NPR. Including only incident OAC treatments could also have been an option since patients with prevalent treatment already often have proven themselves not to bleed. However, this would have led to the risk of comparing prevalent, untreated AF with incident OAC treated AF, where the latter group probably has a higher risk of both stroke and bleeding. Even so, in the sensitivity analyses of OAC

naïve patients, the risk of stroke was lower in the warfarin group and therefore it doesn't seem to be a big problem comparing the two groups.

The most important confounder in all four studies is confounding by indication. Despite adjustments for factors that can influence a physician's choice to anticoagulate- or not, or which drug to use, it is impossible to mitigate such bias in the way an RCT will. This confounding is partially dealt with by adjustments in paper I-III, but there definitely is residual confounding. Study IV is the perfect example of confounding by indication; the two treatment groups (PAC and no PAC) are very different regarding risk of thrombosis and bleeding; with high risk of thrombosis in the PAC group and low risk of thrombosis in the control group, which makes the results difficult to interpret. Due to few patients in each group, we did not go further adjusting for different risk factors for VTE.

Another important confounder probably present in paper I-III is time-varying confounding by previous exposure. When updating covariates over time, it is possible that some are affected by the exposures that we are studying and becomes mediators of the effect. For example, warfarin has been associated with greater decline in kidney function compared to DOAC (191). If the feedback loop between warfarin and poor kidney function was strong, there could be a problem with adjusting GFR over time since some of the warfarin effect might be adjusted away. This can be dealt with using marginal structures, where the most common is inverse-probability-of-treatment-weighting (192).

In papers I-III we adjusted for known risk factors for bleeding, but the use of antiplatelet agents is not accounted for and might contribute to the bleeding risk, especially in patients without OAC. Investigating this further would be of interest.

Competing risk

A competing event is an event that precludes the event of interest from occurring. This is of particular interest in research on subjects with CKD G5-G5D, who are at high risk of competing events, for example death. In paper I-III, the cumulative incidence of the primary events (ischemic stroke and major bleeding) was presented with Kaplan-Meier curves, one curve for each event. In these, patients who died were censored. A problem with censoring for a competing event is that it violates the assumption that censoring should be independent. The Kaplan-Meier (KM) estimates assume that censored individuals are still at risk of the event of interest, in these studies stroke or major bleeding. If a patient is

deceased, these primary events cannot occur, subsequently the censoring is not independent. If competing risks, in our study for example death, is present, KM curves tend to overestimate the cumulative incidence of the event (193). Therefore, if we were to focus on absolute risks in the papers, it would have been more appropriate to present Cumulative Incidence Functions (CIF) (194). The CIF denotes the probability of the occurrence of an event in a setting where each specific event is treated as an absorbing state, the event of interest is only accounted for if occurring before the occurrence of another event. Presenting CIFs, all curves sum up to a composite curve of all events treated as an absorbing state.

In paper I-III a cause-specific Cox proportional hazards model was created for each outcome, censoring for the competing event, death. Cause-specific Cox regression models describe the hazard, the instantaneous rate, of occurrence of the event in patients who still are at risk of the event, i.e. are currently event free from the event of interest or the competing events (194). Another model for dealing with competing risk is the subdistribution hazards model, also called the Fine-Gray method. The Fine-Gray method presents the hazard of an event of interest but as opposed to Cox Regression, patients who experienced a competing event are still considered at risk. The cause-specific models are considered more appropriate for etiological research when trying to make associations between the exposure and the outcomes, as in study I-III. The subdistribution hazards function is suggested to be more appropriate for making predictions of a patients risk of an event (195).

Estimating GFR

All studies used $eGFR_{Cr}$ for estimating kidney function. The golden standard for drug dosing has been estimating GFR by the CG formula. However, CG is rarely used in Sweden and has repeatedly been showed to perform inferior to newer equations. Instead, GFR is estimated with various equations where the Revised Lund-Malmö formula is often used in Sweden and is the equation used in paper IV. In paper I-III the eGFR presented was the eGFR obtained from SRR, where the MDRD formula is used. An important limitation with eGFR by MDRD is that it tends to overestimate GFR in advanced CKD and in the elderly (20). Another consideration with MDRD from SRR is the default assumption that all patients are “non-black” (as opposed to African American). In especially the US, there is an ongoing lively debate if ethnicity should be removed from the eGFR equations due to obvious problems in classifying people by skin color. Therefore a “race-free” CKD-EPI formula was introduced (196). However, this is proven inferior in a European setting, overestimating the eGFR of “non-black” patients and underestimating the eGFR in “black” Europeans (197). The Revised Lund-Malmö formula

doesn't include race, neither does the European Kidney Function Consortium (EKFC) equation. EKFC has been recently introduced and performs well across age-spans and in different ethnical groups in a European setting. Even though the Swedish population is mainly non-black, attention should be given to this issue, since the populations change over time, and old truths should be challenged. An alternative to MDRD in papers I-III would have been to use S-creatinine and calculate eGFR with an equation more appropriate for the target cohort.

Measurement of S/P-albumin

Albumin was measured with BCG-method until November 4th 2013 in Västernorrland, and after this BCP-method was used. BCP is thought to present a few units lower S/P-albumin than BCG and mixing the methods is a limitation. We assessed that the difference was marginal and since the local guidelines for treatment with PAC remained the same, the change of method was disregarded in paper IV.

Conclusions

Warfarin and DOAC are previously proven effective in G3 in RCTs, with lower risk of bleeding on DOAC. In G4, the sparse data from RCTs together with convincing observational data, including ours, do not contradict that this also applies in G4. In G5 and G5D the role of OAC is more uncertain due to the lack of studies proving its safety and efficacy. Our studies with high quality warfarin treatment suggest that warfarin is effective regarding stroke prevention, more convincing in G5D than G5. The risk benefit ratio is however uncertain due to particularly high risk of bleeding in G5/G5D. Patients with high risk of stroke and low risk of bleeding might benefit from warfarin treatment, but only if high TTR is achieved, preferably >70%. Importantly, TTR decreases with GFR decline, and mean TTR in G5/G5D often does not reach this level. Also, the possibility of accelerated vascular calcification and calciphylaxis associated with warfarin is a major concern.

DOAC aren't yet approved for use in G5-G5D, but are a compelling alternative to warfarin. DOAC seem associated with lower, or at least similar, risk of bleeding and comparable risk of ischemic stroke. A signal of increased risk of death on DOAC needs to be investigated further.

Due to the severely increased risk of bleeding irrespective of OAC treatment or abstained treatment, OAC should not be prescribed routinely in NVAF and G5-G5D. RCTs comparing OAC and no OAC need to prove its efficacy and risks in G5-G5D, and to whom it might be beneficial. Patients with very high assessed risk of bleeding should probably be withheld OAC treatment. Awaiting RCTs, it is reasonable to use OAC in selected patients on dialysis, with low risk of bleeding and high risk of ischemic stroke as part of the prevention of cardiovascular disease and death. If choosing warfarin, close monitoring of the treatment is recommended. DOAC seems to be an appealing alternative to warfarin.

The risk of venous thrombosis is high in primary glomerular causes of nephrotic syndrome with an elevated risk during time with S/P-albumin<20g/L. Prophylactic anticoagulants might be warranted in these cases, at least in membranous nephropathy or when other risk factors for VTE are present. However, the risk of bleeding might also be elevated in severe hypoalbuminemia, and bleeding risk on PAC must be weighed against the risk of thrombosis, especially in advanced CKD. The quality of evidence regarding the role of PAC in NS is very low and an RCT comparing PAC and no anticoagulants is called for. Nephrotic

syndrome is also associated with higher risk of arterial events, but further studies need to prove the efficacy and safety of antiplatelet agents as primary prophylaxis before it can be widely recommended.

Future perspectives

The choice of DOAC or warfarin is important. An even more important is if the high risk of bleeding outweighs the possible benefit of stroke prophylaxis in G5-G5D. There are several ongoing RCTs on OAC compared to no treatment in G5-G5D, putting the spotlight on this matter. The Canadian phase 2 open label RCT SAFE-D (Strategies for the Management of Atrial Fibrillation in patiEnts Receiving Dialysis), NCT03987711, compares Apixaban with both VKA and no treatment in G5D. The recruitment is completed but no results are published yet. The open label RCT DANWARD (Danish Warfarin Dialysis Study), NCT03862859, is currently recruiting patients on dialysis to either warfarin or no treatment. The Swedish open label RCT SACK (Stroke prophylaxis with Apixaban in Chronic Kidney disease stage 5 patients with atrial fibrillation), NCT05679024, is also recruiting and compares low dose apixaban with no anticoagulants in G5-G5D. If these studies are successful in their recruitment, they will contribute with very important knowledge. Hopefully, there might finally come uniform, clear guidelines for how to manage patients with NVAF and CKD G5-G5D. Also, these studies will contribute to better understanding of to whom OAC should be prescribed and to whom to abstain. This might result in tailored scoring systems for stroke and bleeding in patients with CKD G5-G5D. Furthermore, there are signals that apixaban might be less dialyzable by peritoneal dialysis than hemodialysis, therefore studies comparing dialysis modalities also need to be performed (198).

Other future therapeutic agents in pipeline are factor XI (FXI) inhibitors. FXI is predominantly involved in the amplification phase of coagulation and plays a role in consolidation of clots, but has no role in the initiation phase (199). Patients with hemophilia C, congenital deficiency of FXI, are prone to bleeding after surgery or trauma, but seldom experience life-threatening bleedings. Furthermore, these patients have lower risk of VTE and ischemic stroke. These properties of FXI suggested a new target for intervention. Indeed, phase II trials of FXI inhibitors have shown promising results with low rates of major bleeding. FXI-inhibitors have in common that they are minimally or not at all cleared by the kidneys. There are two completed phase II studies in G5D of the FXI-inhibitors IONIS-FXIRx and xisomab 3G3 with no major safety concerns (200, 201). The phase II AZALEA-TIMI 71 trial, NCT04755283, compared the FXI inhibitor abelacimab to rivaroxaban in patients with AF and moderate to high risk of stroke. This trial was halted early due to a surprisingly large reduction in major bleedings with abelacimab, but the results aren't published yet. These drugs do sound promising, but

large phase III trials need to prove their safety and efficacy, also in advanced CKD.

Left atrial appendage closure, LAAC, is in theory a compelling alternative to OAC. Long-term results have shown non-inferiority to DOAC and less nonprocedural major bleedings in a general AF population (202). However, no RCT comparing its efficacy and safety to OAC in advanced CKD has been published so far. The single arm prospective Watch-HD trial, NCT03446794, has completed its recruitment, but no results are published yet. SAFE-LAAC CKD, NCT05660811, is currently recruiting comparing single- and double antiplatelet inhibition after LAAC. LACC is an invasive procedure and comes with risk of periprocedural complications. This calls for caution in patients with advanced CKD, an often frail population. It needs to be proven that the postprocedural antiplatelet therapy (even single) is superior to OAC in terms of safety – and that the procedure is beneficial compared to no OAC.

Anticoagulants (or LAAC) is for sure not the only path forward for stroke prevention in AF and CKD. Focus should be turned to what else we can do for our patients for reducing their risk of stroke, looking beyond OAC. Blood pressure- and blood glucose control, SGLT-2 inhibitors (also on dialysis?), physical activity, weight control, oversee alcohol- and smoking habits are examples of important interventions with a more beneficial safety profile.

Should patients with CKD (especially advanced CKD) be screened for atrial fibrillation? Screening for AF is not recommended in Sweden in general but in a population were ¼ has AF, often asymptomatic, this should be investigated- but only if there is an effective and safe treatment.

Regarding anticoagulants in nephrotic syndrome there is much necessary to be done. RCTs need to examine different regimes of PAC versus no treatment in MN and in other primary causes of NS. PAC regimes include LMWH versus warfarin, and DOAC versus warfarin. FXI inhibitors might also be a future alternative. Also, duration of treatment needs to be established as well as the risk of VTE (and arterial thrombosis) depending on subtype causing NS. These studies probably demand international collaboration to recruit enough patients. Furthermore, studies need to examine the benefit and risks with antiplatelet agents in NS.

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Department of Public Health and Clinical Medicine
Umeå universitet, 901 87 Umeå
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