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Pietro Gianella

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ORIGINAL ARTICLE

Stroke and Bleeding in Atrial Fibrillation with Chronic Kidney Disease

Jonas Bjerring Olesen, M.D., Gregory Y.H. Lip, M.D.,
Anne-Lise Kamper, M.D., D.M.Sc., Kristine Hommel, M.D.,
Lars Køber, M.D., D.M.Sc., Deirdre A. Lane, Ph.D.,
Jesper Lindhardsen, M.D., Gunnar Hilmar Gislason, M.D., Ph.D.,
and Christian Torp-Pedersen, M.D., D.M.Sc.

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Background

a) - Atrial fibrillation increases the risk of stroke by a factor of **5**

b) - CKD increases the risk of stroke by a factor of **3.7**

- End-stage renal disease increases the risk of stroke by a factor of **5.8**

Atrial Fibrillation Investigators
Risk factors for stroke and efficacy of antithrombotic therapy in AF: analysis of pooled data from five randomized controlled trials.
Arch Intern Med 1994;154:1449-57.

Lee M, Saver JL, Chang KH, Liao HW, Chang SC, Ovbiagele B.
Low glomerular filtration rate and risk of stroke: meta-analysis.
BMJ 2010;341:c4249.

Background

a) Warfarin may increase the risk of ***ischemic stroke*** among patients with atrial fibrillation and undergoing dialysis (HR 1.93)

b) Risk of ***bleeding*** associated with warfarin treatment is increased among patients with AF who also have CKD

c) Large randomized trials of antithrombotic therapy in patients with AF have excluded those who also have moderate-to-severe CKD

Chan KE, Lazarus JM, Thadhani R, Hakim RM.
Warfarin use associates with increased risk for stroke in hemodialysis patients with AF
J Am Soc Nephrol 2009;20:2223-33.

Wizemann V, Tong L, Satayathum S, et al.
AF in hemodialysis patients: clinical features and associations with anticoagulant therapy.
Kidney Int 2010;77:1098-106.

Yang F, Chou D, Schweitzer P, Hanon
S. Warfarin in haemodialysis patients with atrial fibrillation: what benefit?
Europace 2010;12:1666-72.

Reinecke H, Brand E, Mesters R, et al.
Dilemmas in the management of atrial fibrillation in chronic kidney disease.
J Am Soc Nephrol 2009;20:705-11.

Objective

1. Determine the ***risk*** of
- Stroke
- Systemic thromboembolism
- Bleeding

associated with CKD among patients with AF.

2. Determine whether the ***effect*** of warfarin and aspirin differed between patients
- with CKD
- without CKD

Outcomes

Hospitalization or death from:

1. stroke
2. systemic thromboembolism (peripheral-artery embolism ischemic stroke, and TIA)
3. bleeding (gastrointestinal, intracranial, urinary tract, and airway bleeding)
4. myocardial infarction
5. death from any cause

Methods

Retrospective registry studies in Denmark
- Central Population Registry, the National Patient Registry
- Registry of Medicinal Product Statistics, the
- National Registry on Regular Dialysis and Transplantation
- National Registry of Causes of Death

All patients discharged from the hospital with a diagnosis of ***non-valvular AF*** during the study period, 1997 - 2008

The baseline assessment and follow-up period began **7** days after discharge
- because treatment may have been changed or intensified during or immediately after hospitalization

Methods

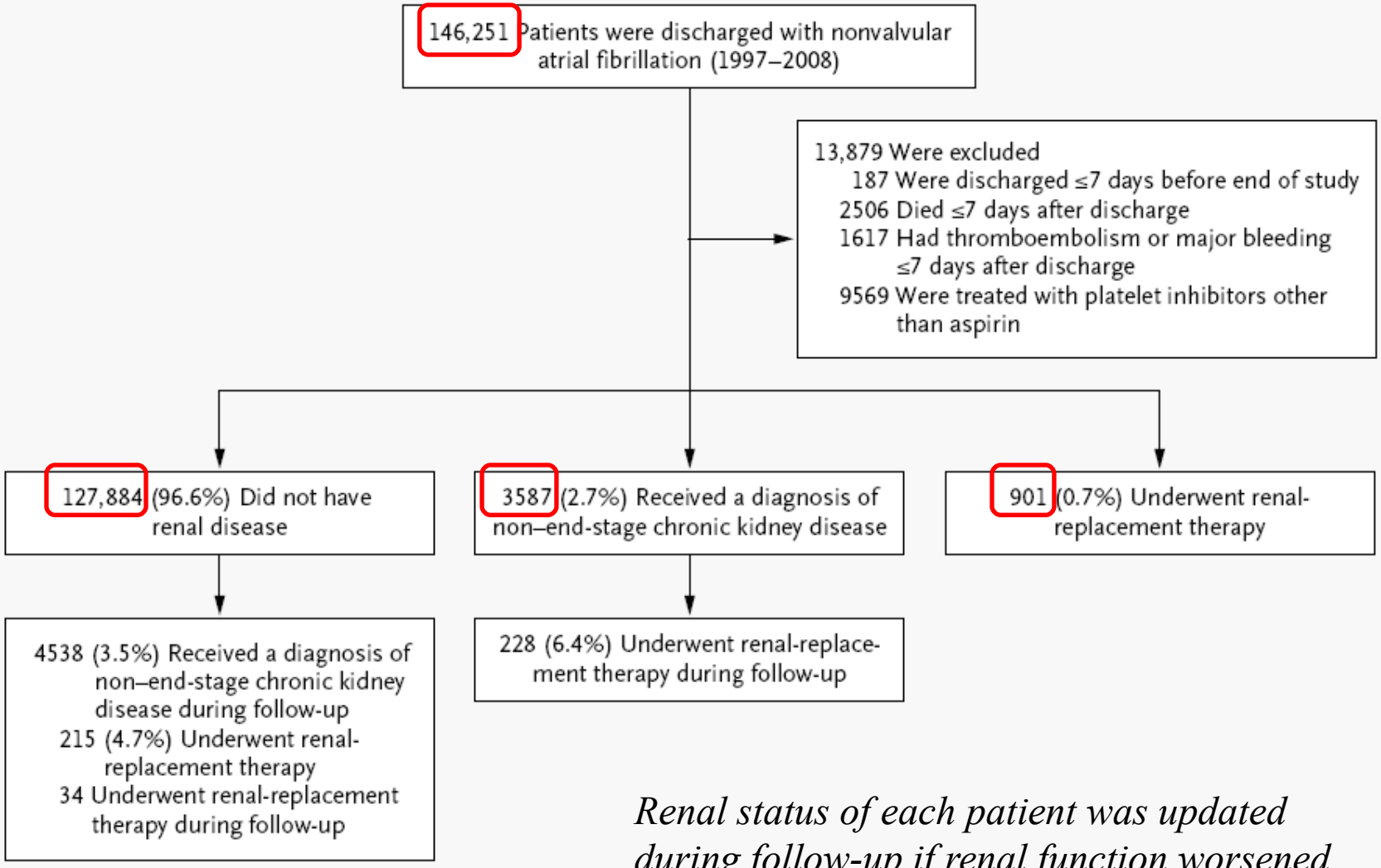
Exclusion criteria

1. Patients receiving antiplatelet drugs other than aspirin
   (i.e., clopidogrel or dipyridamole)

2. Patient who died < 7 days after discharge

3. Patient who had thromboembolism or major bleeding < 7 days after discharge

Methods



Renal status of each patient was updated during follow-up if renal function worsened

Methods

The predicted risk of stroke or systemic thromboembolism was assessed with:

- **C**ardiac Failure or Ejection Fraction ≤35%
- **H**ypertension
- **A**ge (≥ 75 y **2** pts)
- **D**iabetes
- **S**troke, TIA or Systemic Emboli (**2** pts)
- **Va**scular disease (previous MI, peripheral arterial disease or aortic plaque)
- **S**ex (women 1 pts)

The predicted risk of bleeding was assessed with:

- **H**ypertension (>160 mmHg)
- ~~**A**bnormal renal function~~ (since chronic kidney disease was the subject of the study)
- **A**bnormal liver function
- **S**troke
- **B**leeding
- ~~**L**abile INRs~~ (because these data were not available)
- **E**lderly (age ≥ 65)
- **D**rug Therapy (concomitant therapy such as antiplatelet, NSAID's) or Alcohol intake

Methods

Cox analyses were adjusted for:

- CHA2DS2-VASc score
  congestive heart failure, HTA, age >75 years, DM, history of stroke or thromboembolism, vascular disease, female sex

- HAS-BLED
  HTA, abnormal liver function, history of stroke or thromboembolism, history of bleeding, age ≥65 years, use of nonsteroidal antiinflammatory drugs, and unhealthy alcohol use

- Antithrombotic treatment

- Year of inclusion

Table S3. Baseline medications for patients with atrial fibrillation according to renal disease status at baseline

	No renal disease (n=127,884)	Non-end-stage chronic kidney disease (n=3,587)	Renal replacement therapy (n=901)	p-value
Concomitant medication, n (%)				
Adrenergic α-antagonist	1,689 (1.3)	107 (3.0)	47 (5.2)	<0.001
Non-loop-diuretics	42,946 (33.6)	1,444 (40.3)	72 (8.0)	<0.001
Vasodilators	3,926 (3.1)	144 (4.0)	44 (4.9)	<0.001
Beta blockers	56,090 (43.9)	1,507 (42.0)	514 (57.1)	<0.001
Calcium channel blockers	36,160 (28.3)	1,240 (34.6)	441 (49.0)	<0.001
RASi	39,217 (30.7)	1,616 (45.1)	384 (42.6)	<0.001
Loop-diuretics	47,154 (36.9)	2,375 (66.2)	557 (61.8)	<0.001
Statins	15,295 (12.0)	673 (18.8)	187 (20.8)	<0.001
Digoxin	61,284 (47.9)	1,592 (44.4)	302 (33.5)	<0.001
Amiodarone	4,101 (3.2)	137 (3.8)	34 (3.8)	0.08

RASi: Renin-angiotensin system inhibitors

Results _ CHADS2VAS2C

Table 1. Baseline Characteristics of the Patients.*

Characteristic	No Renal Disease (N=127,884)	Non–End-Stage Chronic Kidney Disease (N=3587)	Disease Requiring Renal-Replacement Therapy (N=901)	P Value
Age — yr	73.2±12.9	76.5±11.0	66.8±11.7	<0.001
Risk factors for stroke or thromboembolism — no. (%)				
Congestive heart failure	22,073 (17.3)	1284 (35.8)	171 (19.0)	<0.001
Hypertension	53,917 (42.2)	1952 (54.4)	486 (53.9)	<0.001
Age				
≥75 yr	66,675 (52.1)	2277 (63.5)	267 (29.6)	<0.001
65–74 yr	31,245 (24.4)	809 (22.6)	293 (32.5)	<0.001
Diabetes mellitus	10,920 (8.5)	885 (24.7)	129 (14.3)	<0.001
History of stroke or systemic thromboembolism	17,928 (14.0)	644 (18.0)	133 (14.8)	<0.001
Vascular disease	18,174 (14.2)	1034 (28.8)	248 (27.5)	<0.001
Female sex	59,930 (46.9)	1472 (41.0)	303 (33.6)	<0.001

Results
HASBLED

Table 1. Baseline Characteristics of the Patients.*

Characteristic	No Renal Disease (N=127,884)	Non–End-Stage Chronic Kidney Disease (N=3587)	Disease Requiring Renal-Replacement Therapy (N=901)	P Value
Risk factors for bleeding — no. (%)				
Hypertension	53,917 (42.2)	1952 (54.4)	486 (53.9)	<0.001
Abnormal liver function	2,070 (1.6)	106 (3.0)	36 (4.0)	<0.001
History of stroke or systemic thromboembolism	17,928 (14.0)	644 (18.0)	133 (14.8)	<0.001
History of bleeding	8,969 (7.0)	584 (16.3)	137 (15.2)	<0.001
Age ≥65 yr	95,418 (74.6)	3035 (84.6)	533 (59.2)	<0.001
Use of NSAIDs	26,592 (20.8)	843 (23.5)	99 (11.0)	<0.001
Alcohol abuse	4,552 (3.6)	145 (4.0)	43 (4.8)	0.05
Antithrombotic medication — no. (%)				
Warfarin only	36,638 (28.6)	609 (17.0)	178 (19.8)	<0.001
Aspirin only	23,952 (18.7)	879 (24.5)	153 (17.0)	<0.001
Warfarin and aspirin	10,745 (8.4)	290 (8.1)	45 (5.0)	<0.001
CHA_2DS_2-VASc score†				<0.001
0	11,720 (9.2)	70 (2.0)	42 (4.7)	
1	16,926 (13.2)	251 (7.0)	165 (18.3)	
≥2	99,238 (77.6)	3266 (91.1)	694 (77.0)	
HAS-BLED score‡				<0.001
0 or 1	51,262 (40.1)	883 (24.6)	390 (43.3)	
2	46,159 (36.1)	1336 (37.2)	312 (34.6)	
≥3	30,463 (23.8)	1368 (38.1)	199 (22.1)	

Results

IM (HR)

CKD vs non CKD

2.00

95% CI, 1.86 to 2.16; P<0.001

CKD-HD vs no CKD

3.00

95% CI, 2.58 to 3.50; P<0.001

DEATH (HR)

CKD vs non CKD

2.37

95% CI, 2.30 to 2.44; P<0.001

HR CKD-HD vs no CKD

3.35

95% CI, 3.13 to 3.58; P<0.001

Table 2. Event Rates, According to Status with Respect to Renal Disease.*

Event	No. of Person-yr	No. of Events	Event Rate per 100 Person-yr (95% CI)
Stroke or thromboembolism			
No renal disease	461,734	16,648	3.61 (3.55–3.66)
Non–end-stage CKD	13,078	842	6.44 (6.02–6.89)
Disease requiring renal-replacement therapy	2,922	164	5.61 (4.82–6.54)
Bleeding			
No renal disease	457,605	16,195	3.54 (3.48–3.59)
Non–end-stage CKD	12,515	1,097	8.77 (8.26–9.30)
Disease requiring renal-replacement therapy	2,734	243	8.89 (7.84–10.08)
Myocardial infarction			
No renal disease	480,745	9,037	1.88 (1.84–1.92)
Non–end-stage CKD	13,500	784	5.81 (5.41–6.23)
Disease requiring renal-replacement therapy	2,925	175	5.98 (5.16–6.94)
Death			
No renal disease	493,305	55,297	11.21 (11.12–11.30)
Non–end-stage CKD	14,052	5,431	38.65 (37.63–39.69)
Disease requiring renal-replacement therapy	3,114	914	29.35 (27.51–31.32)

Results

Table 3. Hazard Ratios for Stroke or Systemic Thromboembolism.*

Characteristic	Total Population (N=132,372)		No Renal Disease (N=127,884)†		Non–End-Stage Chronic Kidney Disease (N=3587)†		Disease Requiring Renal-Replacement Therapy (N=901)†	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
All participants			1.00		1.49 (1.38–1.59)	<0.001	1.83 (1.57–2.14)	<0.001
Antithrombotic therapy								
None	1.00		1.00		1.00		1.00	
Warfarin	0.59 (0.57–0.62)	<0.001	0.59 (0.56–0.61)	<0.001	0.84 (0.69–1.01)	0.07	0.44 (0.26–0.74)	0.002
Aspirin	1.11 (1.07–1.15)	<0.001	1.10 (1.06–1.14)	<0.001	1.25 (1.07–1.47)	0.01	0.88 (0.59–1.32)	0.54
Warfarin and aspirin	0.70 (0.65–0.75)	<0.001	0.69 (0.64–0.74)	<0.001	0.76 (0.56–1.03)	0.08	0.82 (0.37–1.80)	0.62
Risk factors for thromboembolism‡								
Congestive heart failure	1.03 (0.99–1.07)	0.18	1.03 (0.99–1.08)	0.11	0.98 (0.84–1.14)	0.78	0.96 (0.64–1.43)	0.84
Hypertension	1.06 (1.03–1.09)	<0.001	1.05 (1.02–1.09)	0.002	1.13 (0.98–1.30)	0.10	1.05 (0.76–1.45)	0.78
Age								
≥75 yr	3.48 (3.31–3.66)	<0.001	3.56 (3.38–3.76)	<0.001	1.87 (1.48–2.36)	<0.001	2.46 (1.60–3.79)	<0.001
65–74 yr	2.02 (1.91–2.14)	<0.001	2.03 (1.92–2.16)	<0.001	1.52 (1.18–1.94)	0.001	2.18 (1.46–3.24)	<0.001
Diabetes	1.32 (1.26–1.38)	<0.001	1.32 (1.25–1.39)	<0.001	1.16 (0.99–1.36)	0.07	1.41 (0.95–2.10)	0.09
History of stroke or systemic thromboembolism	3.20 (3.10–3.31)	<0.001	3.24 (3.14–3.35)	<0.001	2.71 (2.34–3.15)	<0.001	1.99 (1.36–2.91)	<0.001
Vascular disease	1.10 (1.06–1.15)	<0.001	1.12 (1.07–1.16)	<0.001	0.89 (0.76–1.05)	0.17	1.11 (0.78–1.58)	0.57
Female sex	1.12 (1.08–1.15)	<0.001	1.12 (1.08–1.15)	<0.001	1.06 (0.92–1.22)	0.44	1.34 (0.97–1.85)	0.08

Results

Table S4. Distribution of outcome events

Outcome	Number of events (%)			
	Overall	No renal disease	Non-end-stage CKD	Renal replacement therapy
Stroke or systemic thromboembolism	17,654 (100)	16,648 (100)	842 (100)	164 (100)
Non-fatal stroke or thromboembolism	10,682 (60.5)	10,081 (60.6)	496 (58.9)	105 (64.0)
Ischaemic stroke	8,015 (45.4)	7,558 (45.4)	385 (45.7)	72 (43.9)
Peripheral artery embolism	653 (3.7)	595 (3.6)	39 (4.6)	19 (11.6)
Transient ischaemic attack	2,014 (11.4)	1,928 (11.6)	72 (8.6)	14 (8.5)
Fatal stroke or thromboembolism	6,972 (39.5)	6,567 (39.4)	346 (41.1)	59 (36.0)
Ischaemic stroke	6,682 (37.8)	6,301 (37.8)	326 (38.7)	55 (33.5)
Peripheral artery embolism	167 (0.9)	149 (0.9)	14 (1.7)	4 (2.4)
Transient ischaemic attack	123 (0.7)	117 (0.7)	6 (0.7)	0 (0.0)

Results

Table 4. Hazard Ratios for Bleeding.*

Characteristic	Total Population (N=132,372)		No Renal Disease (N=127,884)†		Non–End-Stage Chronic Kidney Disease (N=3587)†		Disease Requiring Renal-Replacement Therapy (N=901)†	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
All participants			1.00		2.24 (2.10–2.38)	<0.001	2.70 (2.38–3.07)	<0.001
Antithrombotic therapy								
None	1.00		1.00		1.00		1.00	
Warfarin	1.28 (1.23–1.33)	<0.001	1.28 (1.23–1.33)	<0.001	1.36 (1.17–1.59)	<0.001	1.27 (0.91–1.77)	0.15
Aspirin	1.21 (1.16–1.26)	<0.001	1.21 (1.16–1.26)	<0.001	1.12 (0.96–1.30)	0.14	1.63 (1.18–2.26)	0.003
Warfarin and aspirin	2.15 (2.04–2.26)	<0.001	2.18 (2.07–2.30)	<0.001	1.63 (1.32–2.02)	<0.001	1.71 (0.98–2.99)	0.06
Risk factors for bleeding‡								
Hypertension	1.01 (0.98–1.04)	0.52	1.01 (0.98–1.04)	0.58	0.99 (0.87–1.11)	0.81	0.92 (0.71–1.20)	0.55
Abnormal liver function	1.37 (1.23–1.52)	<0.001	1.40 (1.25–1.57)	<0.001	1.31 (0.90–1.91)	0.16	0.74 (0.34–1.64)	0.46
History of stroke or systemic thromboembolism	1.23 (1.18–1.28)	<0.001	1.24 (1.19–1.30)	<0.001	1.04 (0.89–1.22)	0.62	0.93 (0.63–1.36)	0.70
History of bleeding	2.44 (2.33–2.55)	<0.001	2.54 (2.42–2.67)	<0.001	1.70 (1.45–1.99)	<0.001	2.09 (1.50–2.91)	<0.001
Age ≥65 yr	2.09 (2.00–2.17)	<0.001	2.12 (2.03–2.20)	<0.001	1.61 (1.35–1.92)	<0.001	1.36 (1.03–1.80)	0.03
Use of NSAIDs	1.12 (1.08–1.16)	<0.001	1.12 (1.08–1.17)	<0.001	1.10 (0.96–1.26)	0.19	0.91 (0.62–1.33)	0.63
Alcohol abuse	1.40 (1.30–1.52)	<0.001	1.43 (1.32–1.56)	<0.001	1.01 (0.73–1.39)	0.97	1.33 (0.70–2.54)	0.39

CKD *vs* no CKD there was an increased risk of bleeding with:

- AVK HR **1.33**; 95% CI, 1.16 to 1.53; P<0.001
- aspirin HR **1.17**; 95% CI, 1.02 to 1.34; P = 0.03
- AVK + aspirin HR **1.61**; 95% CI, 1.32 to 1.96; P<0.001

Results

Table S4. Distribution of outcome events

Outcome	Number of events (%)			
	Overall	No renal disease	Non-end-stage CKD	Renal replacement therapy
Bleeding	17,535 (100)	16,195 (100)	1,097 (100)	243 (100)
Non-fatal bleeding	15,003 (85.6)	13,872 (85.7)	923 (84.1)	208 (85.6)
Gastrointestinal	4,995 (28.5)	4,555 (28.1)	353 (32.2)	87 (35.8)
Intracranial	1,648 (9.4)	1,574 (9.7)	57 (5.2)	17 (7.0)
Urinary tract	4,123 (23.5)	3,768 (23.3)	301 (27.4)	54 (22.2)
Airway	4,237 (24.2)	3,975 (24.5)	212 (19.3)	50 (20.6)
Fatal bleeding	2,532 (14.4)	2,323 (14.3)	174 (15.9)	35 (14.4)
Gastrointestinal	967 (5.5)	863 (5.3)	89 (8.1)	15 (6.2)
Intracranial	1,495 (8.5)	1,401 (8.7)	76 (6.9)	18 (7.4)
Urinary tract	29 (0.2)	22 (0.1)	6 (0.5)	1 (0.4)
Airway	41 (0.2)	37 (0.2)	3 (0.3)	1 (0.4)

Results

Table S6. Risk of stroke or systemic thromboembolism and bleeding associated with level and type of non-end-stage chronic kidney disease in patients with non-valvular atrial fibrillation (n=132,372)

	Frequency	Stroke or systemic thromboembolism		Bleeding	
	N (%)	HR (95% CI)	P value	HR (95% CI)	P value
Patients with no renal disease	127,884 (96.6)*	1 (reference)		1 (reference)	
Non-end-stage CKD (overall)	3,587 (2.7)*	1.49 (1.38-1.59)	<0.001	2.24 (2.10-2.38)	<0.001
Non-end-stage CKD by loop-diuretics†					
Furosemide ≤40 mg/daily	1,820 (22.4)‡	1.40 (1.26-1.54)	<0.001	1.93 (1.76-2.11)	<0.001
Furosemide 40-160 mg/daily	2,760 (34.0)‡	1.60 (1.43-1.80)	<0.001	2.41 (2.17-2.68)	<0.001
Furosemide ≥160 mg/daily	3,545 (43.6)‡	1.52 (1.30-1.79)	<0.001	2.85 (2.51-3.23)	<0.001

The severity of the renal disease was determined by the intensity of treatment with loop diuretics

Results

Table S6. Risk of stroke or systemic thromboembolism and bleeding associated with level and type of non-end-stage chronic kidney disease in patients with non-valvular atrial fibrillation (n=132,372)

	Frequency	Stroke or systemic thromboembolism		Bleeding	
	N (%)	HR (95% CI)	P value	HR (95% CI)	P value
Patients with no renal disease	127,884 (96.6)*	1 (reference)		1 (reference)	
Non-end-stage CKD (overall)	3,587 (2.7)*	1.49 (1.38-1.59)	<0.001	2.24 (2.10-2.38)	<0.001
Non-end-stage CKD by underlying disease					
Adult polycystic kidney disease	224 (2.8)§	1.22 (0.88-1.69)	0.24	1.78 (1.32-2.40)	<0.001
Chronic glomerulonephritis	584 (7.2)§	1.30 (1.03-1.64)	0.03	2.81 (2.40-3.30)	<0.001
Diabetic nephropathy	1,526 (18.8)§	1.41 (1.21-1.65)	<0.001	1.96 (1.70-2.25)	<0.001
Chronic tubulointerstitial nephropathy	875 (10.8)§	1.18 (0.97-1.44)	0.09	1.32 (1.08-1.62)	0.01
Hypertensive nephropathy	282 (3.5)§	1.92 (1.46-2.54)	<0.001	1.82 (1.36-2.43)	<0.001
Other etiology	184 (2.3)	1.43 (0.96-2.14)	0.08	1.38 (0.91-2.10)	0.13
Nephropathy of unknown etiology	4,625 (56.9)	1.60 (1.45-1.76)	<0.001	2.49 (2.29-2.71)	<0.001

Discussion - 1

- Patients with AF *AND* CKD were associated with

increased risks of stroke or systemic thromboembolism and bleeding

- Among patients with <u>non–end-stage chronic kidney disease:</u>

- the ***risk of stroke*** or systemic thromboembolism was not influenced by the severity of the renal disease

- whereas the ***risk of bleeding*** was influenced by the severity of the renal disease

Discussion - 2

- The risks of **myocardial infarction** and **death** from any cause were also increased among patients with AF *AND* CKD as compared with those who had no renal disease.

- **AVK** reduced the risk of stroke or systemic thromboembolism in the whole study population and among patients with CKD
  - whereas **aspirin** did not reduce this risk

Discussion - 3

- Warfarin therapy was associated with a significant reduction in the risk of stroke or thromboembolism among patients with CDK

BUT

the risk of bleeding among such patients was significantly increased

- The net clinical effect of warfarin treatment requires careful assessment in patients with CKD and the data do not provide clear guidance regarding indications for anticoagulant therapy in patients with both **AF** and **CKD**

- Ideally, the role of AVK (or of other, newer anticoagulant agents) in patients with AF who have CKD should be evaluated in a clinical trial

Limitations

❖ Positive predictive value of the diagnosis of AF is very high (99%) the inclusion of only hospitalized patients with AF is likely to have resulted in an **overestimate** of the proportion of patients who were at **increased risk** for thromboembolism and bleeding.

❖ Despite the accuracy of filled prescriptions as a measure of medication use aspirin can also be bought **over the counter** in Denmark, and the use of aspirin may therefore be **underestimated**.

- It is also possible that the increased risk of stroke or systemic thromboembolism that was associated with aspirin was due to **confounding by indication**.

❖ Cox regression: HASBLED, CHADS2VASC2

Conclusion

- Among patients with AF, CKD was independently associated with increased risks of:

- *stroke or systemic thromboembolism*
- *bleeding*
- *myocardial infarction*
- *death*

- ***Aspirin*** was not associated with a reduced risk of stroke or systemic thromboembolism but was associated with an increased risk of bleeding.

- ***Warfarin*** was associated with a decreased risk of stroke or systemic thromboembolism among patients with CKD
  - ***Warfarin + Aspirin*** were associated with an increased risk of bleeding

Opinion - 1

Bleeding risk IRC -> Causes of platelet impairment include:
- intrinsic platelet defects
- abnormal platelet-endothelial interaction
- uremic toxins
- anemia (< 100 g/l)

AVK give only a ~60% protection against stroke
but improved 100% the bleeding risk.

Stroke ≠ Bleeding
- Mortality
- QALY

Mortality/QALY in **CKD-AF** vs **CKD-AF** + AVK

Opinion - 2

Bleeding risk of CKD with AF = bleeding risk CKD

CKD in HASBLED or in CHADSVASC?

Merci pour votre attention

Mount Charro Chalten, Patagonia, Border between Chile and Argentina Height: 3.375 m