

**Supplementary Table 1: Searching strategy**

Database	Searching strategy
PubMed	(("Atrial Fibrillation"[Mesh]) AND "Rivaroxaban"[Mesh]) AND (((((((Acute kidney injury) OR (≥30% decreasing in estimated glomerular filtration rate)) OR (Doubling of the serum creatinine level)) OR (Kidney failure)) OR (Progress to end stage of renal disease)) OR (Need haemodialysis)) OR (Need or a kidney transplant))
EMBASE	('atrial fibrillation'/exp OR 'atrial fibrillation' OR 'atrium fibrillation' OR 'auricular fibrillation' OR 'auricular fibrillation' OR 'cardiac atrial fibrillation' OR 'cardiac atrium fibrillation' OR 'fibrillation, heart atrium' OR 'heart atrial fibrillation' OR 'heart atrium fibrillation' OR 'heart fibrillation atrium' OR 'non-valvular atrial fibrillation' OR 'nonvalvular atrial fibrillation') AND (rivaroxaban/exp OR '5 chloro n [ [2 oxo 3 [4 (3 oxomorpholin 4 yl) phenyl] 1, 3 oxazolidin 5 yl] methyl] thiophene 2 carboxamide' OR '5 chloro n [ [2 oxo 3 [4 (3 oxomorpholin 4 yl) phenyl] oxazolidin 5 yl] methyl] thiophene 2 carboxamide' OR '5 chloro n [ [2 oxo 3 [4 (3 oxomorpholino) phenyl] 5 oxazolidinyl] methyl] 2 thiophenecarboxamide' OR 'aban (drug)' OR 'assubex' OR 'ast 8294' OR 'ast8294' OR 'bay 59 7939' OR 'bay 59-7939' OR 'bay 597939' OR 'bay59 7939' OR 'bay59-7939' OR 'bay597939' OR 'bs 112' OR 'bs112' OR 'dst 8294' OR 'dst8294' OR 'jnj 39039039' OR 'jnj39039039' OR 'kriva' OR 'naxat' OR 'rivar' OR 'rivarolto' OR 'rivaroxaban' OR 'rivaxa' OR 'throsaben' OR 'xanirva' OR 'xarelto' OR 'xerdoxo' OR 'xindus') AND ('acute kidney injury' OR ('kidney failure'/exp OR 'kidney failure' OR 'kidney insufficiency' OR 'maternal kidney failure' OR 'renal failure' OR 'renal insufficiency' OR 'terminal kidney failure') OR 'decreasing in estimated glomerular filtration rate' OR 'Doubling of the serum creatinine level' OR 'Progress to end-stage of renal disease' OR haemodialysis OR ('kidney transplantation'/exp OR 'kidney allograft transplantation' OR 'kidney allotransplantation' OR 'kidney cadaver transplantation' OR 'kidney grafting' OR 'kidney homotransplantation' OR 'kidney retransplantation' OR 'kidney transplantation' OR 'renal homotransplantation' OR 'renal transplantation' OR 'second set kidney transplantation' OR 'transplantation, kidney'))
Cochrane Library	(rivaroxaban):ti,ab,kw AND ("atrial fibrillation"):ti,ab,kw

**Supplementary Table 2:** Main characteristics of the included studies

Study ID	Type of publication	Design	Study population	N	Interventional arm	Control arm	Examined outcomes
Bonnemeier 2019 - diabetes <sup>1</sup>	Conference abstract	Retrospective, claim database	Patients with NVAF and diabetes	21845	NOACs Rivaroxaban (N = 6997) Apixaban (N = 5438) Edoxaban (N = 865)	Phenprocoumon (N = 8545)	<ul style="list-style-type: none"> <li>• End stage renal disease</li> <li>• Acute kidney injury</li> <li>• Ischemic stroke/systemic embolism</li> <li>• Intracranial haemorrhage</li> <li>• Fatal bleeding</li> </ul>
Bonnemeier 2019 - renal disease <sup>2</sup>	Conference abstract	Retrospective, claim database	Patients with NVAF and renal disease	17842	NOACs Rivaroxaban (N = 5121) Apixaban (N = 4750) Edoxaban (N = 682)	Phenprocoumon (N = 7289)	<ul style="list-style-type: none"> <li>• End stage renal disease</li> <li>• Acute kidney injury</li> <li>• Ischemic stroke/systemic embolism</li> <li>• Intracranial haemorrhage</li> <li>• Fatal bleeding</li> </ul>
Chan 2018 <sup>3</sup>	Article	Retrospective cohort study	Patients with NVAF	75221	NOACs Rivaroxaban (N = 28066) Apixaban (N = 5875) Dabigatran (N = 20145)	Warfarin (N = 21135)	<ul style="list-style-type: none"> <li>• Acute kidney injury</li> </ul>
Coleman 2019 <sup>4</sup>	Article	Retrospective, claim database	Patients with NVAF	72599	Rivaroxaban (N = 36318)	Warfarin (N = 36281)	<ul style="list-style-type: none"> <li>• Acute kidney injury</li> <li>• Progression to stage 5 CKD or need for hemodialysis</li> <li>• Ischemic stroke/systemic embolism</li> <li>• Major bleeding</li> </ul>
Costa 2021 <sup>5</sup>	Article	Retrospective, electronic health record analysis	Patients with NVAF and type 2 diabetes	83182	Rivaroxaban (N = 24912)	Warfarin (N = 58270)	<ul style="list-style-type: none"> <li>• &gt;40% decrease in eGFR from baseline</li> <li>• eGFR &lt; 15 mL/minute, need for dialysis, renal transplant</li> <li>• Major adverse limb event</li> <li>• Retinopathy</li> <li>• All-cause mortality</li> </ul>
González 2022 <sup>5</sup>	Article	Retrospective, electronic health record analysis	Patients with NVAF and eGFR $\geq$ 50 ml/min/1.73m <sup>2</sup>	11652	Rivaroxaban (N = 5338)	Warfarin (N = 6314)	<ul style="list-style-type: none"> <li>• Doubling of serum creatinine</li> <li>• <math>\geq</math>30% decline in eGFR</li> <li>• Incidence of ESRD</li> </ul>
Harel 2021 <sup>7</sup>	Article	Retrospective, population-based cohort study	Outpatients $\geq$ 66 years with AF	20683	NOACs Rivaroxaban (N = 5263) Apixaban (N = 8217) Dabigatran (N = 2277)	Warfarin (N = 4926)	<ul style="list-style-type: none"> <li>• Acute kidney injury</li> <li>• All-cause mortality</li> </ul>
Hernandez 2020 <sup>8</sup>	Article	Retrospective, claim database	Patients with NVAF and diabetes	21682	Rivaroxaban (N = 10017)	Warfarin (N = 11665)	<ul style="list-style-type: none"> <li>• Acute kidney injury</li> <li>• Progression to stage 5 CKD or need for haemodialysis</li> </ul>
Klil-Drori 2017 <sup>9</sup>	Conference abstract	Retrospective, population-based cohort study	Patients with NVAF	26357	NOACs (N = not available) Rivaroxaban Apixaban Dabigatran	Warfarin (N = not available)	<ul style="list-style-type: none"> <li>• Acute kidney injury</li> </ul>

Kreutz 2023 <sup>10</sup>	Conference abstract	Prospective, observational study	NVAF patients with an eGFR of 15-49 mL/min/1.73 m <sup>2</sup>	1455	Rivaroxaban (N = 764)	Warfarin (N = 691)	<ul style="list-style-type: none"> <li>• A composite of eGFR decline to &lt;15 mL/min/1.73 m<sup>2</sup>, need for chronic kidney replacement therapy or development of acute kidney injury</li> <li>• Stroke or systemic embolism, major bleeding, myocardial infarction, acute coronary syndrome, or cardiovascular death</li> </ul>
Lee 2023 <sup>11</sup>	Article	Retrospective, population-based cohort study	Patients with AF	47946	Rivaroxaban (N = 17013)	Warfarin (N = 30933)	<ul style="list-style-type: none"> <li>• Kidney failure</li> <li>• eGFR lower than 15 ml/min/1.73 m<sup>2</sup></li> <li>• Starting dialysis or having kidney transplantation</li> <li>• ≥ 30% decline in eGFR</li> <li>• Doubling of serum creatinine level</li> <li>• Acute kidney injury</li> <li>• Ischemic stroke, intracranial hemorrhage, major gastrointestinal bleeding, major bleeding, and all-cause mortality.</li> </ul>
Shahzada 2022 <sup>12</sup>	Article	Retrospective cohort study	Patients with NVAF	600	NOACs Rivaroxaban (N = 200) Apixaban (N = 100) Dabigatran (N = 100)	Warfarin (N = 200)	<ul style="list-style-type: none"> <li>• ≥30% decline in eGFR</li> <li>• Doubling of serum creatinine</li> <li>• Kidney failure</li> </ul>
Vaitsiakhovich 2022 <sup>13</sup>	Article	Observational, retrospective, cohort study	Patients with AF and moderate-to-severe CKD	7368	Rivaroxaban (N = 1465)	Warfarin (N = 5903)	<ul style="list-style-type: none"> <li>• Composite of progression to CKD stage 5, kidney failure, or need for dialysis.</li> </ul>
Yao 2017 <sup>14</sup>	Article	Retrospective cohort study	Patients with NVAF	9769	NOACs Rivaroxaban (N = 2485) Apixaban (N = 1883) Dabigatran (N = 1216)	Warfarin (N = 4185)	<ul style="list-style-type: none"> <li>• ≥30% decline in eGFR</li> <li>• Doubling of the serum creatinine level</li> <li>• Acute kidney injury</li> <li>• Kidney failure</li> </ul>

### Abbreviations:

AF – atrial fibrillation; NVAF - Non-valvular atrial fibrillation; CKD - Chronic kidney disease; eGFR - Estimated glomerular filtration rate; NOACs - Non-Vitamin K oral anticoagulants

**Supplementary Table 3:** Risk of bias assessment of included studies

	<b>Bias due to confounding</b>	<b>Bias in selection of participants into the study</b>	<b>Bias in classification of interventions</b>	<b>Bias due to deviations from intended interventions</b>	<b>Bias due to missing data</b>	<b>Bias in measurement of outcomes</b>	<b>Bias in selection of the reported result</b>	<b>Overall</b>
Bonnemeier 2019 – diabetes <sup>1</sup>	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Bonnemeier 2019 - renal disease <sup>2</sup>	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Chan 2018 <sup>3</sup>	Low risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Moderate risk
Coleman 2019 <sup>4</sup>	Low risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Moderate risk
Costa 2021 <sup>5</sup>	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
González 2022 <sup>6</sup>	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Harel 2021 <sup>7</sup>	Low risk	Low risk	Low risk	Low risk	Serious risk	Low risk	Low risk	Serious risk
Hernandez 2020 <sup>8</sup>	Low risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Moderate risk
Klil-Drori 2017 <sup>9</sup>	Serious	Low risk	Low risk	Low risk	Serious	Serious	Low risk	Serious risk
Kreutz 2023 <sup>10</sup>	Low risk	Low risk	Low risk	Low risk	No information	Low risk	Low risk	Low risk*#
Lee 2023 <sup>11</sup>	Low risk	Low risk	Low risk	Low risk	Serious risk	Low risk	Low risk	Serious risk
Shahzada 2022 <sup>12</sup>	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Vaitsiakhovich 2022 <sup>13</sup>	Low risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Moderate risk
Yao 2017 <sup>14</sup>	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

\* Unclear risk in the domain of missing data.

# Evaluation based on protocol information in addition to information in the abstract

Supplementary Table 4: Sensitive analysis

Acute kidney injury: Rivaroxaban vs VKA			
	Status	HR (95% CI)	p-interaction
Diabetes	Yes	0.71 (0.60 - 0.84)	0.352
	No	0.61 (0.47 , 0.81)	
Renal disease	Yes	0.65 (0.55 - 0.78)	0.361
	No	0.73 (0.61 , 0.87)	
Asian	Yes	0.62 (0.48 - 0.81)	0.303
	No	0.72 (0.64 , 0.80)	
Dosing	20 mg	0.39 (0.19 – 0.77)	0.172
	15 mg	0.66 (0.5 – 0.88)	

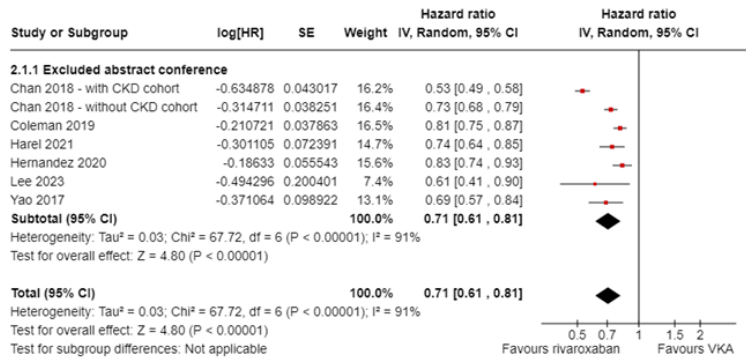
≥30% decrease in eGFR: Rivaroxaban vs VKA			
	Status	HR (95% CI)	p-interaction
Diabetes	Yes	0.75 (0.58 - 0.96)	0.398
	No	0.43 (0.12 , 1.51)	
Renal disease	Yes	0.54 (0.23 - 1.29)	0.941
	No	0.56 (0.36 , 0.86)	
Asian	Yes	0.53 (0.23 - 1.24)	0.323
	No	0.82 (0.67 , 1.00)	

Doubling of serum creatinine : Rivaroxaban vs VKA			
	Status	HR (95% CI)	p-interaction
Diabetes	Yes	0.63 (0.46 - 0.87)	0.330
	No	0.42 (0.20 – 0.90)	
Renal disease	Yes	0.41 (0.17 - 1.00)	0.483
	No	0.57 (0.44 , 0.73)	
Asian	Yes	0.42 (0.20 - 0.88)	0.423
	No	0.58 [0.44 , 0.76]	

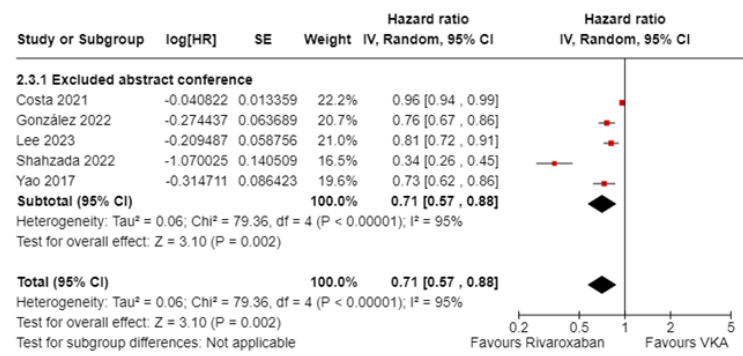
Worsening renal function: Rivaroxaban vs VKA			
	Status	HR (95% CI)	p-interaction
Diabetes	Yes	0.59 (0.43 - 0.80)	0.476
	No	0.50 (0.36 , 0.70)	
Renal disease	Yes	0.48 (0.37 - 0.63)	0.660
	No	0.54 (0.34 , 0.84)	
Asian	Yes	0.40 (0.32 - 0.51)	<b>0.007</b>
	No	0.61 (0.50 , 0.75)	
Dosing	20 mg	0.77 (0.29 -2.04)	0.423
	15 mg	0.51 (0.39 – 0.65)	

# Supplementary Figure 1: Forest plot of sensitive analyses

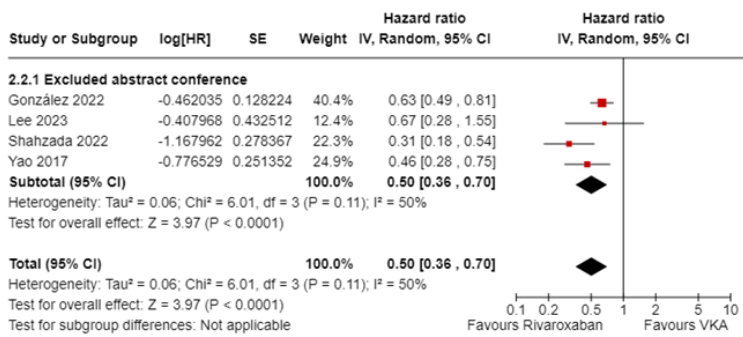
## Supplement – Figure 1A. Acute kidney injury



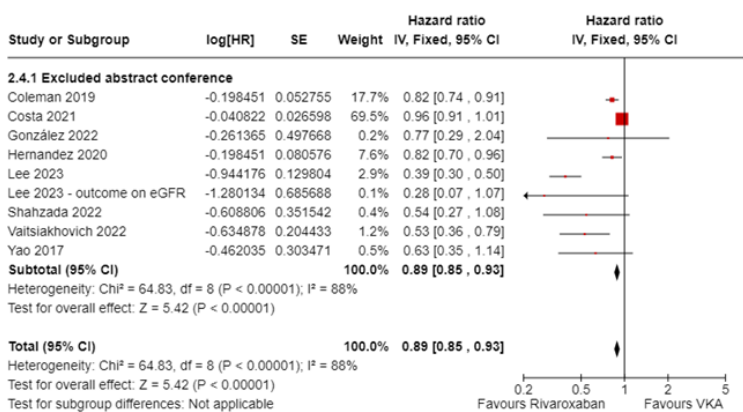
## Supplement - Figure 1B. ≥30% decrease in eGFR



## Supplement – Figure 1C. Doubling of serum creatinine

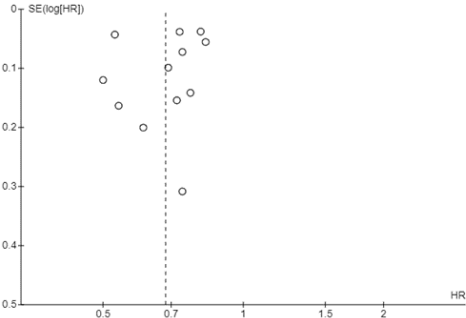


## Supplement – Figure 1D. Worsening renal function

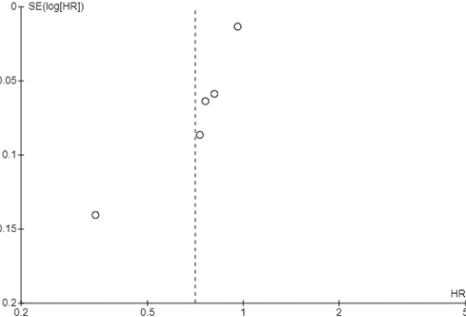


**Supplementary Figure 2: Funnel plot for assessment of publication bias**

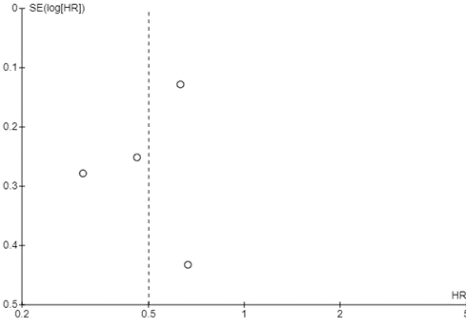
**A. Acute kidney injury**



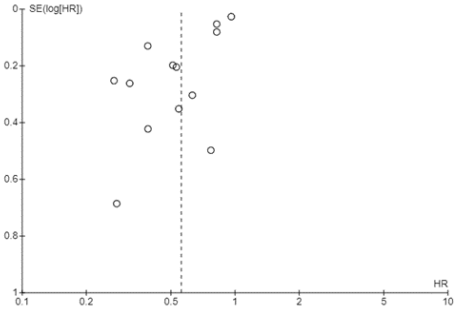
**B. ≥30% decrease in eGFR**



**C. Doubling of serum creatinine**



**D. Worsening renal function**



## References:

1. Bonnemeier H, Kreutz R, Kloss S, Enders D, Häckl D, Schmedt N. Comparative safety and effectiveness of non-vitamin-K oral anticoagulants vs phenprocoumon in patients with non-valvular atrial fibrillation and diabetes—results from the RELOADed study. *Eur Stroke J*. 2019;4(1\_suppl):1–860.
2. Bonnemeier H, Kreutz R, Kloss S, Enders D, Häckl D, Schmedt N. Comparative safety and effectiveness of non-vitamin-K oral anticoagulants vs phenprocoumon in patients with non-valvular atrial fibrillation and renal disease—results from the RELOADed study. *Eur Stroke J*. 2019;4(1\_suppl):1–860.
3. Chan YH, Yeh YH, Hsieh MY, Chang CY, Tu HT, Chang SH, et al. The risk of acute kidney injury in Asians treated with apixaban, rivaroxaban, dabigatran, or warfarin for non-valvular atrial fibrillation: A nationwide cohort study in Taiwan. *International Journal of Cardiology*. 2018 Aug 15;265:83–9.
4. Coleman CI, Kreutz R, Sood N, Bunz TJ, Meinecke AK, Eriksson D, et al. Rivaroxaban's Impact on Renal Decline in Patients With Nonvalvular Atrial Fibrillation: A US MarketScan Claims Database Analysis. *Clin Appl Thromb Hemost*. 2019 Jan 1;25:1076029619868535.
5. Costa OS, O'Donnell B, Vardar B, Abdelgawwad K, Brescia CW, Sood N, et al. Kidney, limb and ophthalmic complications, and death in patients with nonvalvular atrial fibrillation and type 2 diabetes prescribed rivaroxaban or warfarin: an electronic health record analysis. *Current Medical Research and Opinion*. 2021 Sep 2;37(9):1493–500.
6. González Pérez A, Balabanova Y, Sáez ME, Brobert G, García Rodríguez LA. Renal decline in patients with non-valvular atrial fibrillation treated with rivaroxaban or warfarin: A population-based study from the United Kingdom. *International Journal of Cardiology*. 2022 Apr 1;352:165–71.
7. Harel Z, McArthur E, Jeyakumar N, Sood MM, Garg AX, Silver SA, et al. The Risk of Acute Kidney Injury with Oral Anticoagulants in Elderly Adults with Atrial Fibrillation. *Clinical Journal of the American Society of Nephrology*. 2021 Oct;16(10):1470.
8. Hernandez AV, Bradley G, Khan M, Fratoni A, Gasparini A, Roman YM, et al. Rivaroxaban vs. warfarin and renal outcomes in non-valvular atrial fibrillation patients with diabetes. *European Heart Journal - Quality of Care and Clinical Outcomes*. 2020 Oct 1;6(4):301–7.
9. Klil-Drori AJ, Azoulay L, Nie R, Renoux C, Nessim SJ, Filion KB. Comparative Risk of Acute Kidney Injury with Oral Anticoagulant Use Among Patients with Nonvalvular Atrial Fibrillation. *Blood*. 2017 Dec 7;130(Supplement 1):700.
10. Kreutz RH. RIVAROXABAN ASSOCIATES WITH REDUCED RISK OF ADVERSE KIDNEY OUTCOMES IN COMPARISON TO VITAMIN K ANTAGONIST TREATMENT IN A PROSPECTIVE REAL-WORLD STUDY IN PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION AND ADVANCED CHRONIC KIDNEY DISEASE. *Journal of the American College of Cardiology*. 2023;81(8\_Supplement):108–108.
11. Lee SR, Choi EK, Park SH, Han KD, Oh S, Abdelgawwad K, et al. Renal outcomes of rivaroxaban compared with warfarin in Asian patients with nonvalvular atrial fibrillation: A nationwide population-



based cohort study. *Frontiers in Cardiovascular Medicine* [Internet]. 2023 [cited 2023 Nov 20];10. Available from: <https://www.frontiersin.org/articles/10.3389/fcvm.2023.1040834>

12. Shahzada TS, Guo CL, Lee APW. Renal outcomes in Asian patients receiving oral anticoagulants for non-valvular atrial fibrillation. *Hong Kong Med J*. 2022 Feb;28(1):24–32.

13. Vaitsiakhovich T, Coleman CI, Kleinjung F, Vardar B, Schaefer B. Worsening of kidney function in patients with atrial fibrillation and chronic kidney disease: evidence from the real-world CALLIPER study. *Current Medical Research and Opinion*. 2022 Jun 3;38(6):937–45.

14. Yao X, Tangri N, Gersh BJ, Sangaralingham LR, Shah ND, Nath KA, et al. Renal Outcomes in Anticoagulated Patients With Atrial Fibrillation. *Journal of the American College of Cardiology*. 2017 Nov 28;70(21):2621–32.