# Managing your NVAF patients beyond stroke prevention
# : Should we care for renal function?

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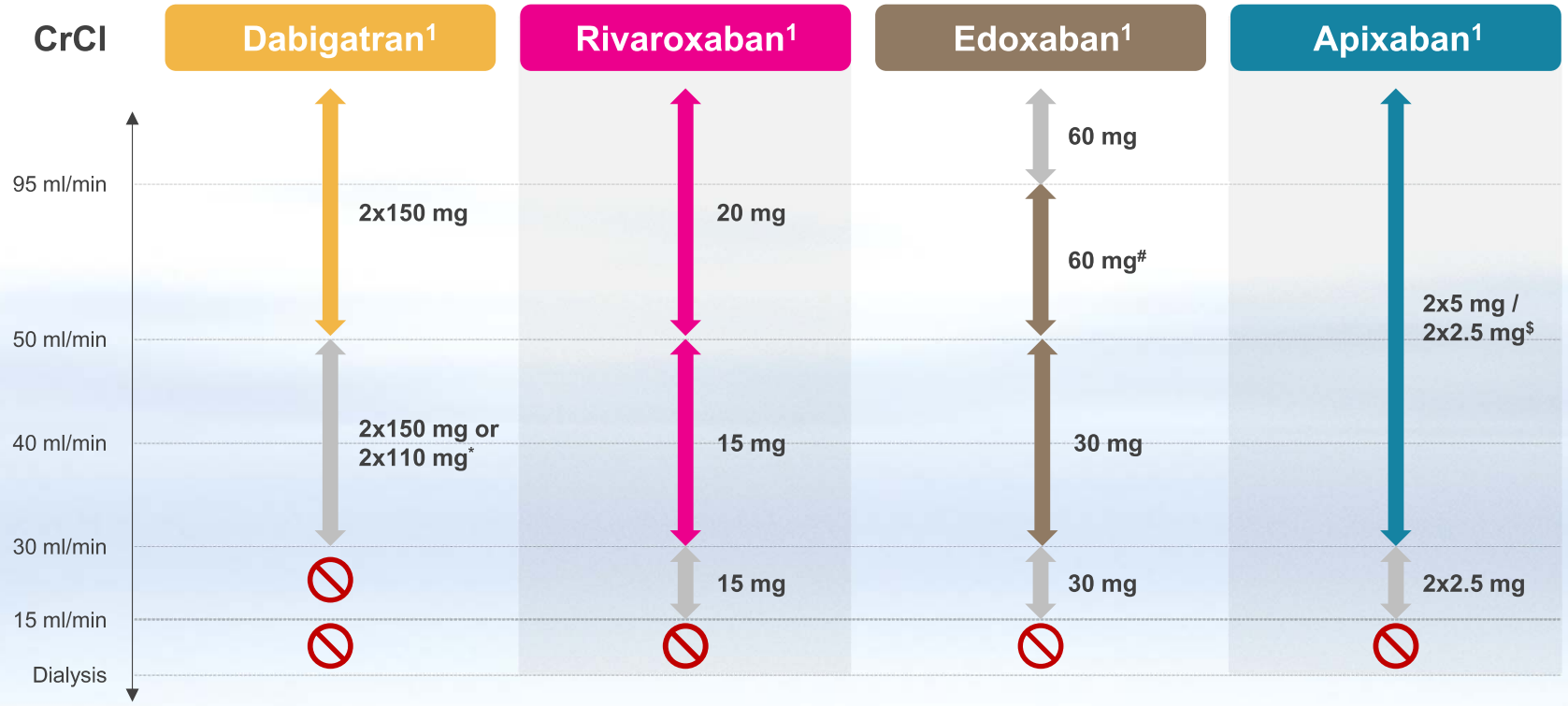
# 2018 EHRA guideline for NOACs and dosing in CKD




EHRA, European Heart Rhythm Association

Use of non-vitamin K antagonist oral anticoagulants according to renal function.
*2X110 mg in patients at high risk of bleeding (per SmPc).
#Other dose reduction criteria may apply (weight ≤60 kg, concomitant potent P-Gp inhibitor therapy).
$2X2.5 mg only if at least two out of three fulfilled: age ≥80 years, body weight ≤60 kg, creatinine ≥1.5 mg/dL (133 mmol/L). Orange arrows indicate cautionary use (dabigatran in moderate renal insufficiency, FXa inhibitors in severe renal insufficiency, edoxaban in 'supranormal' renal function); see text for details.



1. Steffel J, *et al. Eur Heart J* 2018;39:1330-1393.

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# FDA Label Regarding Use of Rivaroxaban 15 mg OD in ESRD Patients on Dialysis

- **Recommended dosage for Rivaroxaban in patients with CrCl ≤ 50 mL/min is 15 mg OD in US.**

**Before Revision on Oct 2018**

| Indication | Dosage | |
|---|---|---|
| Reduction in Risk of Stroke in Nonvalvular Atrial Fibrillation | CrCl >50mL/min | 20 mg once daily with the evening meal |
| | **CrCl 15 to 50mL/min** | **15 mg once daily with the evening meal** |

**After Revision on Oct 2018**

| Indication | Renal Considerations | Dosage | Food/ Timing |
|---|---|---|---|
| Reduction in Risk of Stroke in Nonvalvular Atrial Fibrillation | CrCl >50mL/min | 20 mg once daily | Take with the evening meal |
| | **CrCl ≤50mL/min** | **15 mg once daily** | **Take with the evening meal** |

**Xarelto® is currently not indicated for NVAF patients with CrCl < 15 mL/min in Korea.**

1. Xarelto® USPI. Revised 07/2018. 2. Xarelto® USPI. Revised 10/2018.



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# 2019 AHA/ACC/HRS Guideline for Management of patients with AF

| Recommendations for Selecting an Anticoagulant Regimen—Balancing Risks and Benefits | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| **IIb** | **B-NR** | **For patients with AF who have a $CHA_2DS_2$-VASc score of 2 or greater in men or 3 or greater in women and who have end-stage chronic kidney disease (CKD; creatinine clearance [CrCl] <15 mL/min) or are on dialysis, it might be reasonable to prescribe warfarin (INR 2.0 to 3.0) or apixaban for oral anticoagulation.**<br><br>**MODIFIED**: New evidence has been added. LOE was updated from B to B-NR. (Section 4.1. in the 2014 AF Guideline) |

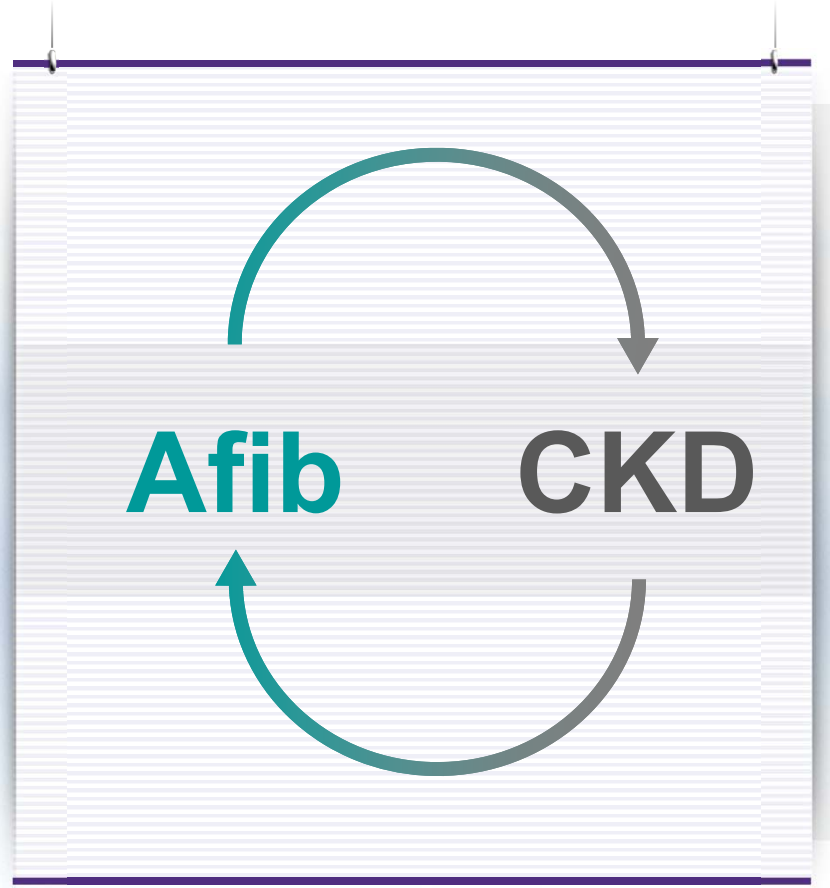

January CT, et al. 2019 Focused Update on Atrial Fibrillation .

# 2019 AHA/ACC/HRS Guideline for Management of patients with AF

| Recommendations for Selecting an Anticoagulant Regimen—Balancing Risks and Benefits | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| **III: No Benefit** | **C-EO** | **In patients with AF and end-stage CKD or on dialysis, the direct thrombin inhibitor dabigatran or the factor Xa inhibitors rivaroxaban or edoxaban are not recommended because of the lack of evidence from clinical trials that benefit exceeds risk.**<br>**MODIFIED**: New data have been included. Edoxaban received FDA approval and has been added to the recommendation. LOE was updated from C to C-EO. (Section 4.1. in the 2014 AF Guideline) |


January CT, et al. 2019 Focused Update on Atrial Fibrillation .

# Correlation of Afib and CKD




- Atrial fibrillation (AF) and chronic kidney disease (CKD) share common risk factors, including older age, hypertension and diabetes mellitus.[1]
- CKD increases the risk of incident AF, whereas AF increases the risk of development and progression of CKD.[1]
- AF and CKD are associated with an increased risk of thromboembolic events; patients with severe CKD also exhibit a paradoxical increase in bleeding risk.[1]



1. Potpara TS, *et al. Nat Rev Nephrol* 2018;14;337-351.

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# Why does kidney disease matter?

- Danish national registries data 1997-2008[1]
- 132,372 patients included; 3,587 patients (2.7%) with non-end-stage CKD[1*]

**Risk comparison for**

**AF patients with non-end-stage CKD[1]** VS. **AF patients without CKD[1]**

**Stroke risk**

**1.49**

(CI: 1.38-1.59; $p < 0.001$)

**Bleeding risk†**

**2.24**

(CI: 2.10-2.38; $p < 0.001$)

*Of the patients with non-end-stage CKD, 1,788/3,587 (50%) received antithrombotic medication at baseline;
†Bleeding risk was assessed using the HAS-BLED score, which reflects the risk of major bleeding among patients with AF who are receiving anticoagulant therapy.
CI=Confidence interval; HAS-BLED=Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding, History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly.

NOAC, non-VKA oral anticoagulant; PD, pharmacodynamic; PK, pharmacokinetic; VKA, vitamin K antagonist.



1. Olesen JB, *et al. N Engl J Med* 2012;367:625-635.

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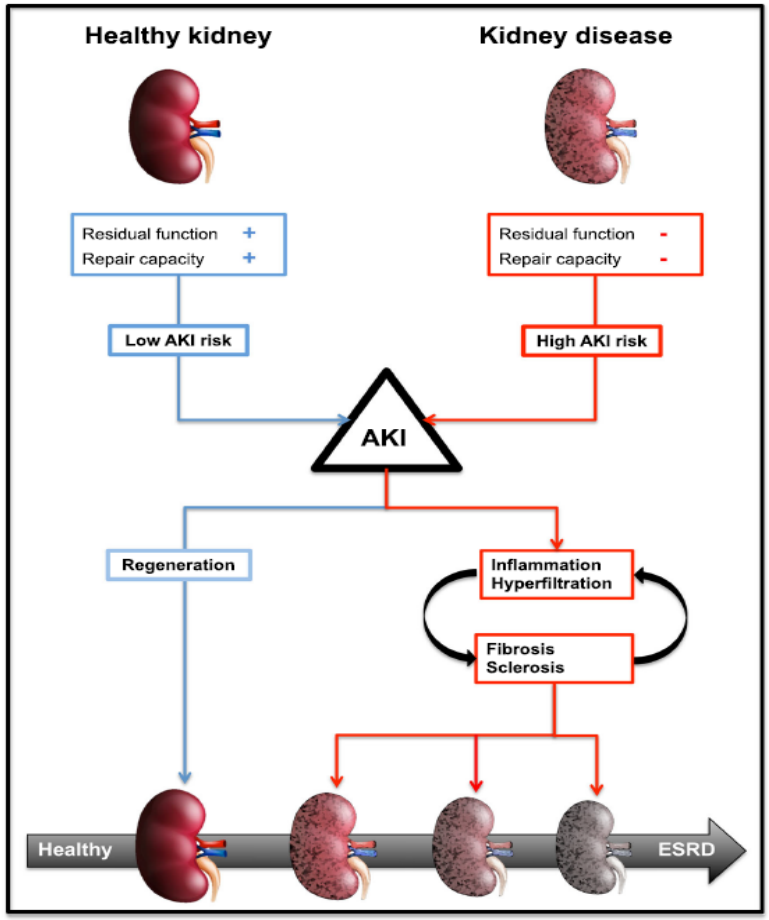
# The Aftermath of AKI

- **AKI** is a frequent complication of hospitalization and is associated with an increased risk of CKD, ESRD and mortality.
- **The impact of AKI on long term adverse outcomes** is highly dependent on the comorbidities, including CVD, HTN, DM, and pre-existing CKD.
- **The main focus of future research** should be on the prevention of AKI, and the provision of adequate f/u and treatment to preserve the renal function of patients who survive an episode of AKI




**A schematic representation of the long-term sequelae of AKI**


Fortrie G et al, Critical Care 2019;23:24

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# 1) Anticoagulant-Related Nephropathy (ARN)

- A type of AKI and possibly, progressive CKD
- Among OAC pts, without underlying kidney disease & moderate~severe anticoagulation (INR >4)
- Other risk factor (multifactorial)
  - CKD, DM, HF, HTN, GN, etc.
- Pathogenesis
  - glomerular haemorrhage
  - obstruction of renal tubules by RBC casts
  - tubular epithelial cell injury

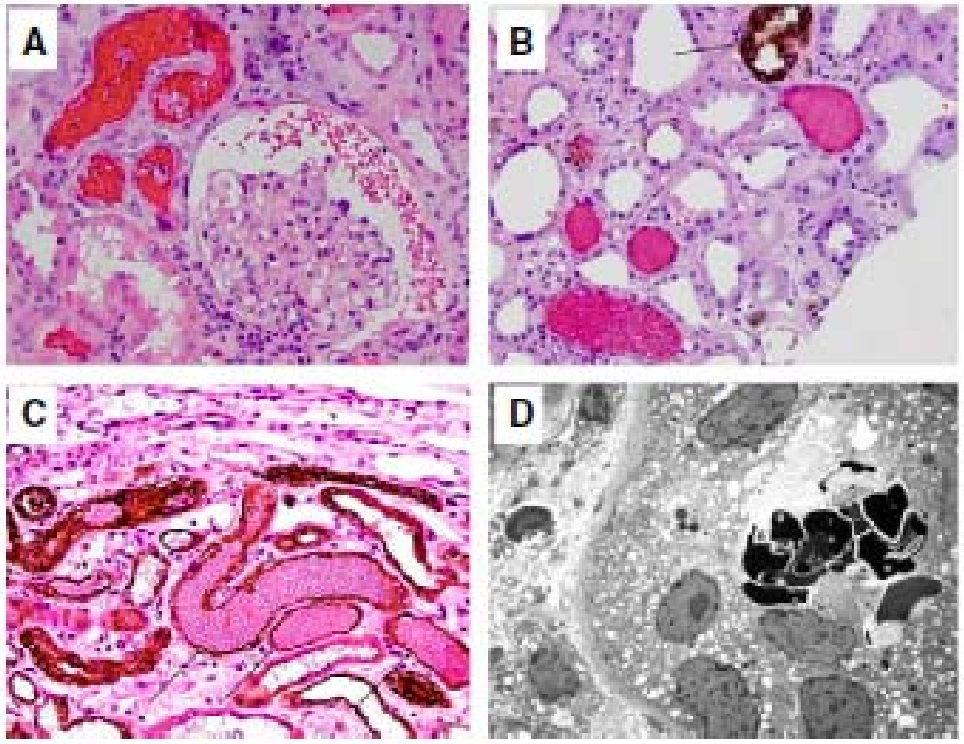


Figure 1. Typical renal biopsy findings in warfarin-related nephropathy. Red blood cells(RBCs) in different compartments of the kidney in patients on warfarin therapy with acute kidney injury. (A) numerous RBCs and RBC occlusive casts were noticed in tubules and Bowman space. (Hematoxylin and eosin statin; original magnification x200). (B) Immuno-histochemical statin for Tamm-Horsfall protein shows that most RBC casts do not contain Tamm-Horsfall protein. (Arrow) Positively-stained thick ascending loop of Henle. (C) Immunohistochemical statin for cytokeratin AE1/AE3 (arrows, dark brown) highlights distal tubules with occlusive RBC casts. (Counterstatin with hematoxylin/eosin; original magnification x200). (D) Dysmorphic RBCs were noticed in several tubules by means of electron microscopy. (Uranyl acetate, lead citrate statin; original magnification x3000).



Brodsky S *et al*, *J Am Soc Nephrol* 2018;29:2787–2793

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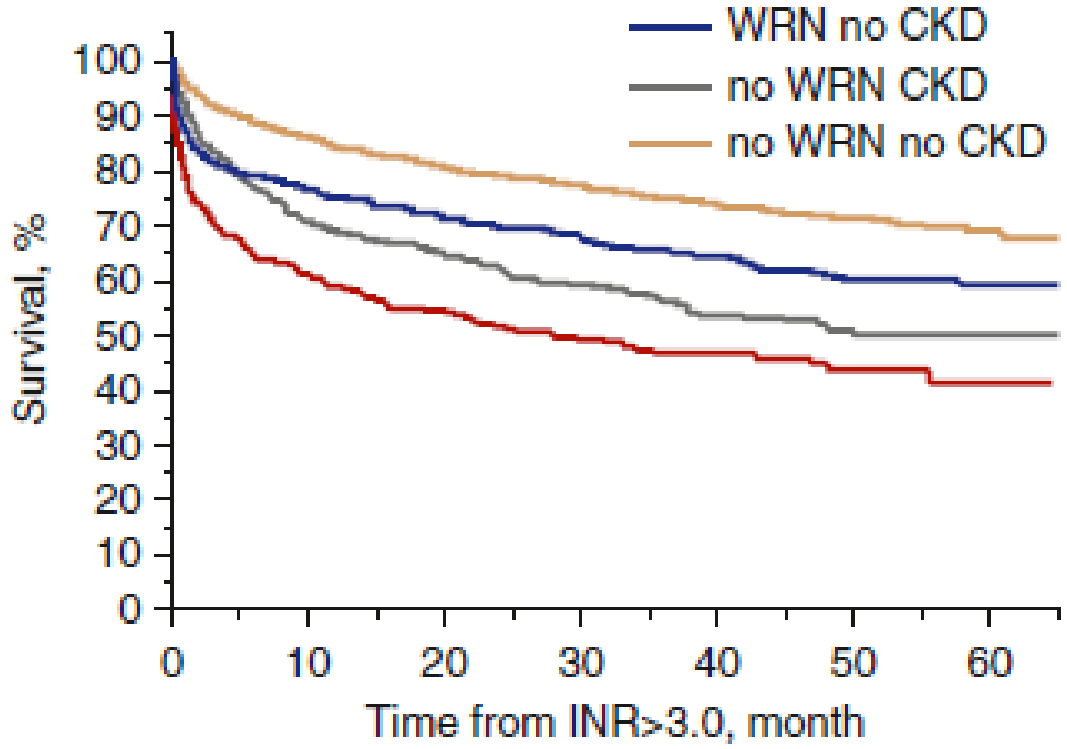
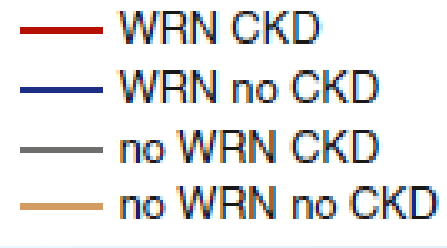
# Presumptive ARN Is Associated with a Marked Increase in Acute Mortality Rate

- Survival rate in a retrospective analysis of 4006 warfarin-treated patients with and without warfarin-related nephropathy (WRN)






Brodsky S *et al*, Kidney Int. 2011 Jul;80(2):181-9. doi: 10.1038/ki.2011.44. Epub 2011 Mar 9.

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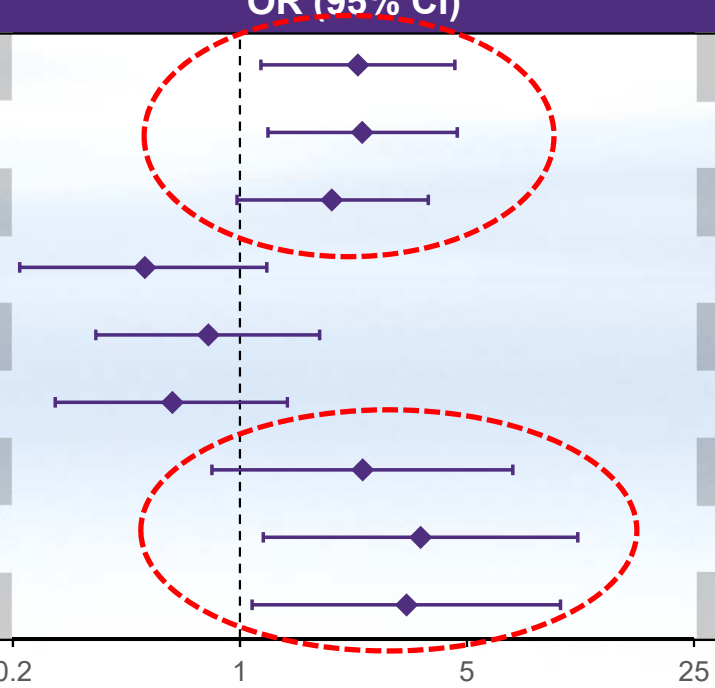
# VKAs, but not NOACs, Contribute to 2) Vascular Calcification

- CT-angiographic analysis of patients with AF with no history of major adverse cardiac or cerebrovascular events (n=236)

| | Site of calcification | OR (95% CI) |
|---|---|---|
| **No anticoagulation vs VKA** | Ascending aorta calcification | 2.31 (1.16–4.59) |
| | Descending aorta calcification | 2.38 (1.22–4.67) |
| | Aortic valve calcification | 1.92 (0.98–3.80) |
| No anticoagulation vs NOAC | Ascending aorta calcification | 0.51 (0.21–1.21) |
| | Descending aorta calcification | 0.80 (0.36–1.76) |
| | Aortic valve calcification | 0.62 (0.27–1.40) |
| **NOAC vs VKA** | Ascending aorta calcification | 2.39 (0.82–6.92) |
| | Descending aorta calcification | 3.60 (1.18–10.97) |
| | Aortic valve calcification | 3.26 (1.09–9.70) |




ORs calculated based on propensity score-adjusted regression analysis

AF, atrial fibrillation; CI, confidence interval; NOAC, non-vitamin K antagonist oral anticoagulant; OR, odds ratio; VKA, vitamin K antagonist



Peeters FECM *et al*, *TH Open* 2018;2:e391–e398

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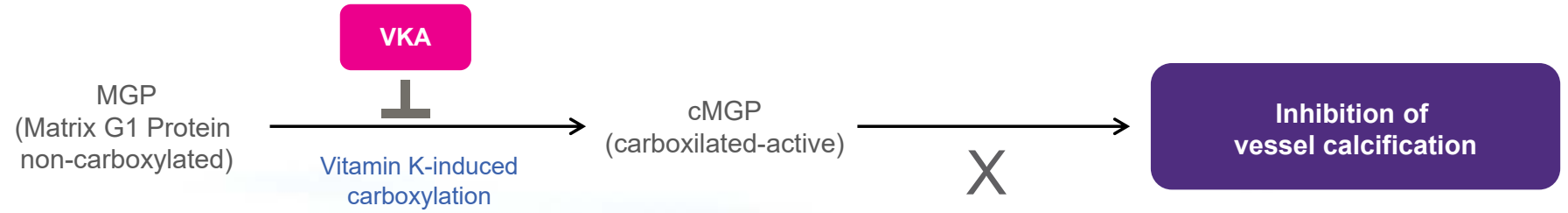
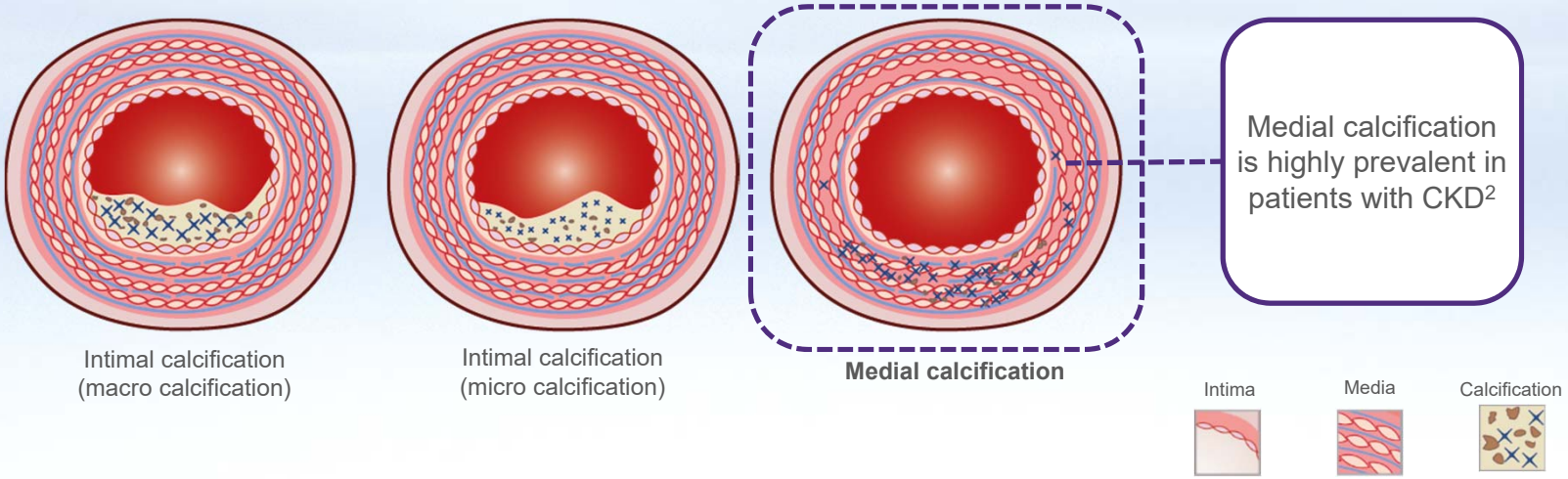
# Vascular injury, calcification and decline in renal function in CKD patients: role of VKDP




MGP is the main inhibitor of vascular calcification, and vitamin K is required for full activity of MGP[1]






1. Van Gorp RH, Schurgers LJ. Nutrient 2015;7:9538–9557; 2. Willems BAG et al. Mol Nutr Food Res 2014;58:1620–1635.

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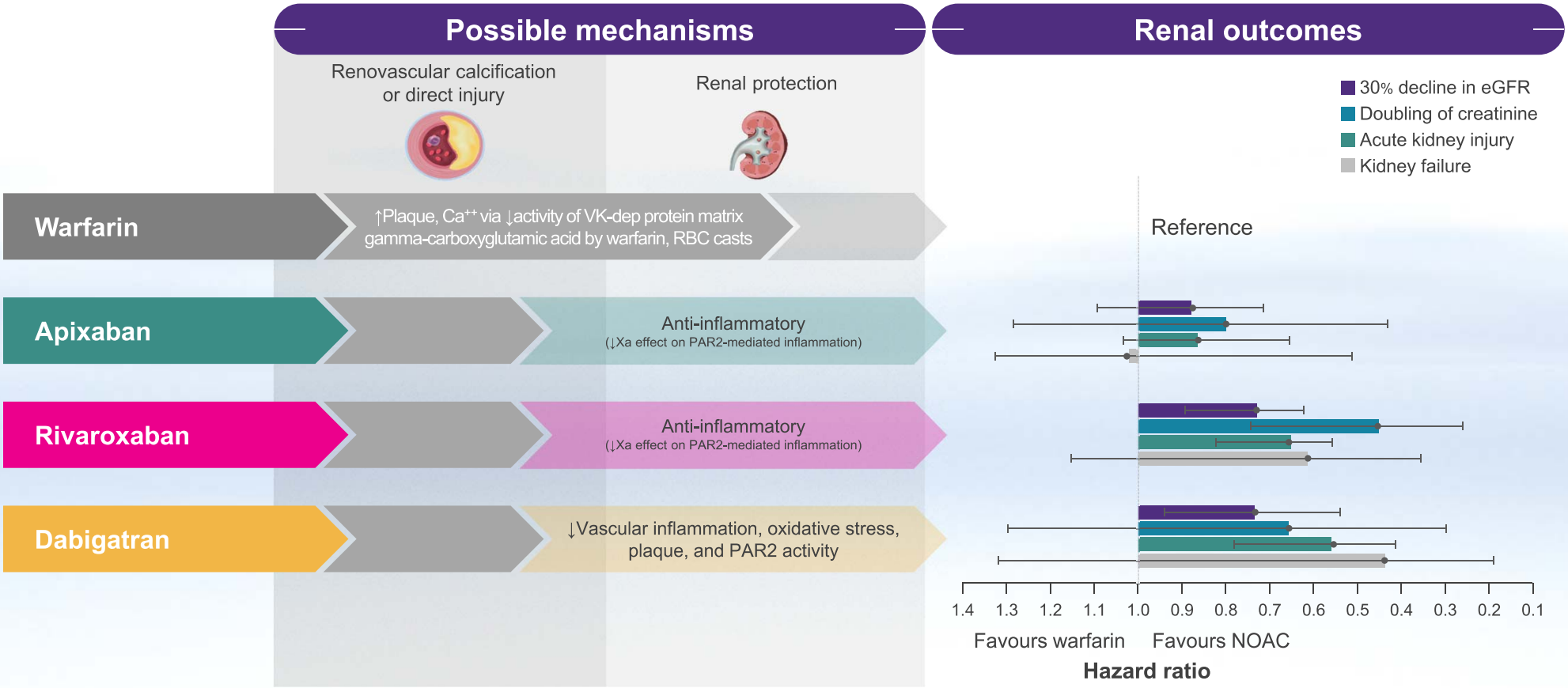
# Possible Mechanisms of NOACs and Renal Outcomes




These data are reflective of real world practice of clinicians
eGFR, estimated glomerular filtration rate; NOAC, non-vitamin K antagonist oral anticoagulant; PAR2, protease-activated receptor 2; RBC, red blood cell; VK, vitamin K.



1. Yao X, *et al. J Am Coll Cardiol* 2017;70:2621-2632.

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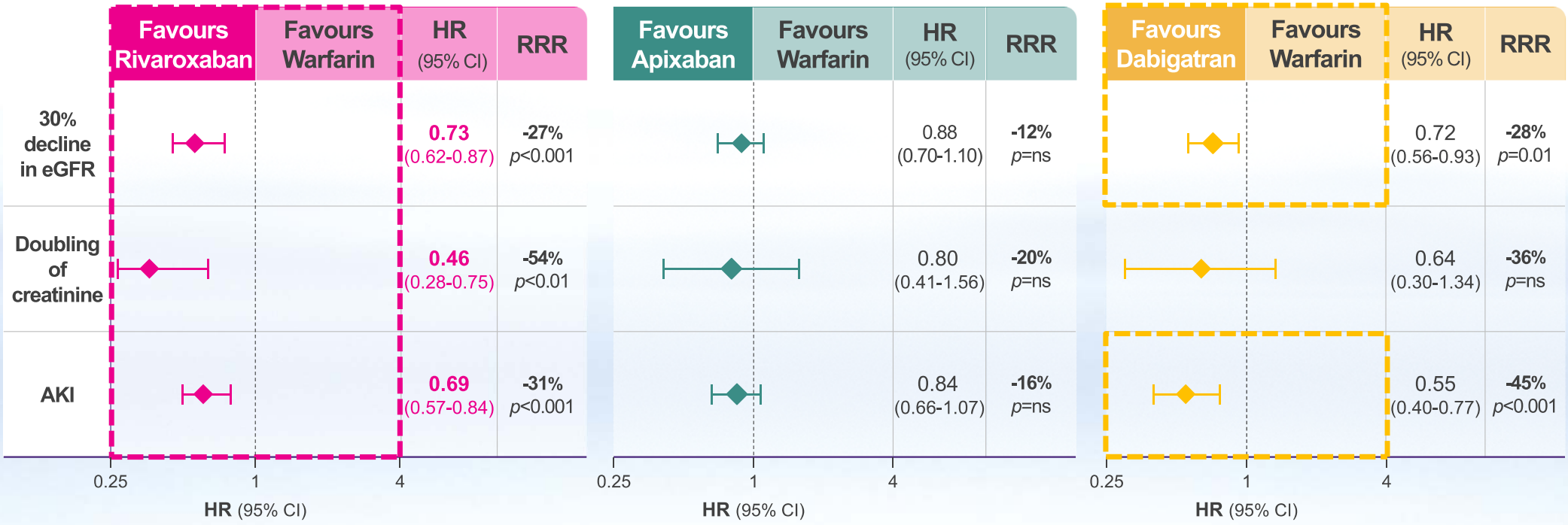
# Rivaroxaban was associated with lower risk of adverse renal outcomes than warfarin




Results are not intended for direct comparison between NOACs. Therefore it should be carefully interpreted.

CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; NOAC, non-vitamin K antagonist oral anticoagulant; RRR, relative risk reduction; AKI, acute kidney injury



1. 1. Yao X, *et al.* J Am Coll Cardiol. 2017 Nov 28;70(21):2621-2632.

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# 2019 AHA/ACC/HRS Guideline for Management of patients with AF

## 4.2.2.2. Non-Vitamin K oral anticoagulants (modified from section 4.2.2.2., "New target-specific oral anticoagulants," in the 2014 AF Guideline

studies, uninterrupted dabigatran had a more favorable outcome than warfarin in ablation of AF (RE-CIRCUIT Trial [Uninterrupted Dabigatran Etexilate in Comparison to Uninterrupted Warfarin in Pulmonary Vein Ablation]) (S4.2.2.2-15). Over time, NOACs (particularly dabigatran and rivaroxaban) may be associated with lower risks of adverse renal outcomes than warfarin in patients with AF (S4.2.2.2-16). Among older adults with AF receiving anticoagulation, dabigatran was associated with a lower risk of

"Over time, **NOACs** (particularly dabigatran and **rivaroxaban**) **may be associated with lower risks of adverse renal outcomes than warfarin** in patients with AF (S4.2.2.2-16)."



January CT, et al. 2019 Focused Update on Atrial Fibrillation

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# Real-world data for renal preservation



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# Rivaroxaban's Impact on Renal Decline in Patients with Non-Valvular Atrial Fibrillation

**RIVAL study**

- To compare rivaroxaban & warfarin's impact on the **development of AKI** and progression to **stage 5 CKD** or need for **hemodialysis** in NVAF patients managed in routine practice
- Retrospective Truven US MarketScan claims database analysis from 2012 to 2017
- naïve NVAF except CKD 5 or hemodialysis
- **Study outcomes**
  - Primary endpoints: Hospital/emergency department visit for AKI and the composite of progression to stage 5 CKD or need for hemodialysis
  - Secondary endpoints: SSE, major bleeding



Coleman, CI et al. Clinical and Applied Thrombosis/Hemostasis, 2019, Vol 25: 1-8 DOI: 10.1177/1076029619868535

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# Rivaroxaban was associated with reductions in progression to AKI and stage 5 CKD vs warfarin

| | Event Rate (per 100 Person-Years) | | | |
|---|---|---|---|---|
| | Rivaroxaban N=36,318 | Warfarin N=36,281 | | HR* (95%CI*) |
| Acute Kidney Injury | 4.91 | 8.45 | | 0.81 (0.75-0.87) |
| Stage 5 CKD* or Dialysis | 2.67 | 4.12 | | 0.82 (0.74-0.91) |

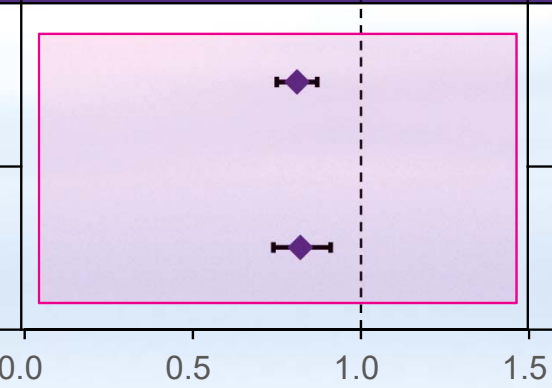


Figure 1. Incidence and Hazard Ratios for Rivaroxaban and Warfarin for Renal Endpoints

CI: confidence interval; CKD: chronic kidney disease; HR: hazard ratio



Coleman, CI et al. Clinical and Applied Thrombosis/Hemostasis, 2019, Vol 25: 1-8 DOI: 10.1177/1076029619868535

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# Rivaroxaban was associated with reductions in Stroke/SE and had comparable major bleeding vs warfarin

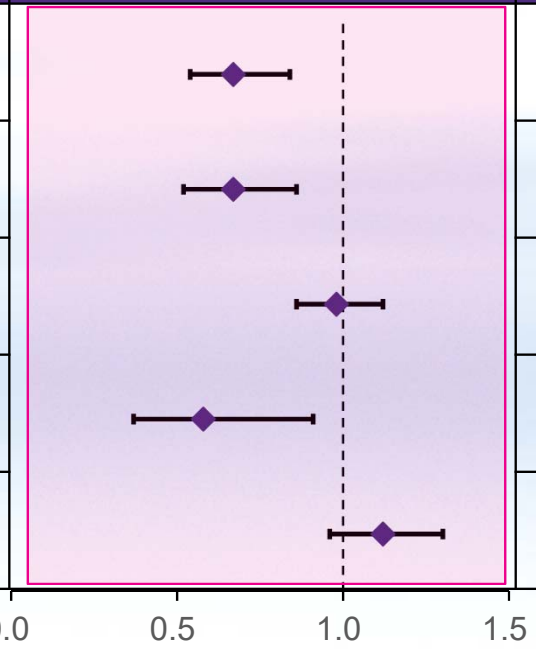
| | Event Rate (per 100 Person-Years) | | | |
|---|---|---|---|---|
| | Rivaroxaban N=36,318 | Warfarin N=36,281 | | HR* (95%CI*) |
| Stroke or SE | 0.62 | 1.19 |  | 0.67 (0.54-0.84) |
| Ischemic Stroke | 0.49 | 0.90 | | 0.67 (0.52-0.86) |
| Major Bleeding | 1.91 | 2.67 | | 0.98 (0.86-1.12) |
| Intracranial | 0.13 | 0.33 | | 0.58 (0.37-0.91) |
| Gastrointestinal | 1.49 | 1.80 | | 1.12 (0.96-1.30) |



Figure 2. Incidence and Hazard Ratios for Rivaroxaban and Warfarin for Secondary Endpoints

CI: confidence interval; CKD: chronic kidney disease; HR: hazard ratio



Coleman, CI et al. Clinical and Applied Thrombosis/Hemostasis, 2019, Vol 25: 1-8 DOI: 10.1177/1076029619868535

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# Worsening of renal function in AF patients with stage 3 or 4 CKD treated with warfarin or rivaroxaban

## CALLIPER study

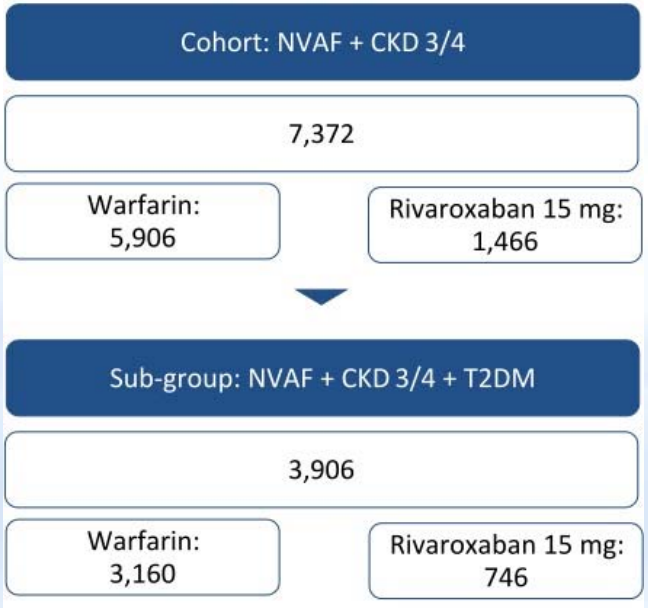
- To investigate the risk of **worsening of renal function** of the reduced dose rivaroxaban 15mg vs. warfarin in patients with renal dysfunction
- US IBM Watson Market Scan claims database from 2012 to 2017
- naïve NVAF with CKD 3 or 4, +/- T2DM
- Study outcome:
  - Primary endpoints: the risk of worsening of renal function

    (progression to CKD stage 5, kidney failure, or need for dialysis)

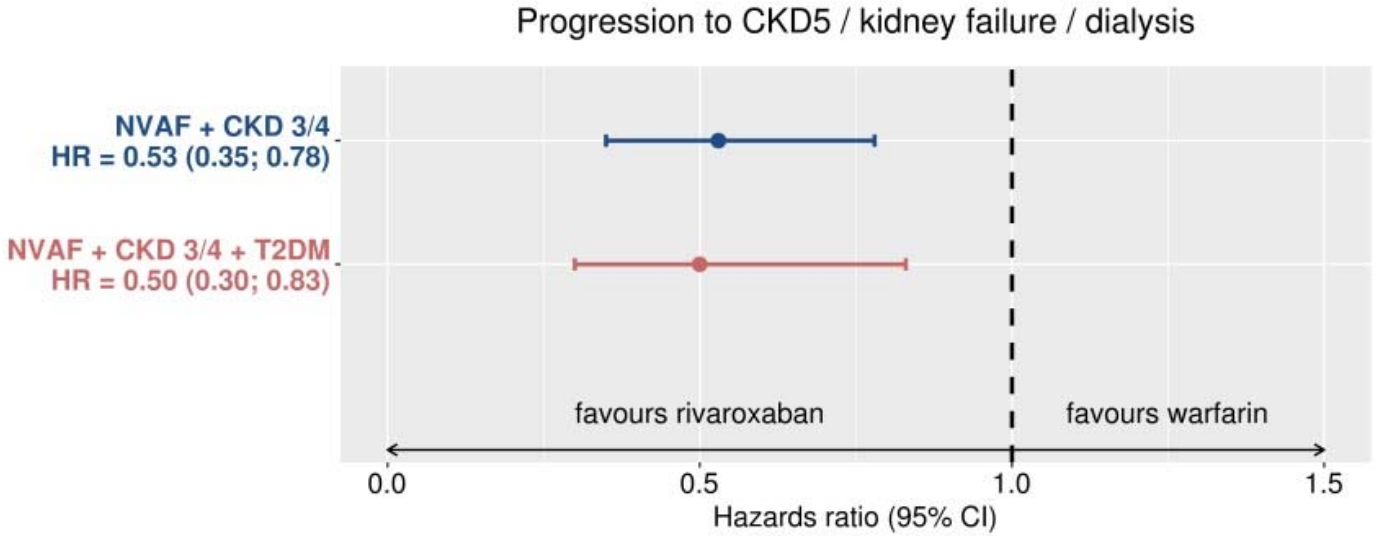


Vaitsiakhovich T, Abstract P4746 presented at ESC, Sep 2019; https://esc365.escardio.org/Congress/ESC-CONGRESS-2019/Poster-Session-5-Atrial-fibrillation-and-oral-anticoagulation-1/199280-worsening-of-renal-function-in-atrial-fibrillation-patients-with-stage-3-or-4-chronic-kidney-disease-treated-with-warfarin-or-rivaroxaban-evidence-from-the-real-world-calliper-study-in-the-us-claims#abstract

# In patients with NVAF and CKD stage 3 and 4, rivaroxaban 15mg significantly lowered the risk of worsening renal function vs warfarin




| Cohort: | Number of patients | | Event rate (per 100 PY) | | Hazard ratio, 95% CI |
|---|---|---|---|---|---|
| | Warfarin | Rivaroxaban 15 mg | Warfarin | Rivaroxaban 15 mg | |
| NVAF + CKD 3/4 | 5,906 | 1,466 | 7.49 | 3.86 | 0.53 (0.35; 0.78) |
| NVAF + CKD 3/4 + T2DM | 3,160 (54%) | 746 (51%) | 10.01 | 4.95 | 0.50 (0.30; 0.83) |




- Median age 79, CHADS2 score 2.67, CHA2DS2VASc score=4.43 (3.405.62), modified HASBLED score=3.00 (2.40 3.65), ≥50% T2DM patients were present

Vaitsiakhovich T, Abstract P4746 presented at ESC, Sep 2019; https://esc365.escardio.org/Congress/ESC-CONGRESS-2019/Poster-Session-5-Atrial-fibrillation-and-oral-anticoagulation-1/199280-worsening-of-renal-function-in-atrial-fibrillation-patients-with-stage-3-or-4-chronic-kidney-disease-treated-with-warfarin-or-rivaroxaban-evidence-from-the-real-world-calliper-study-in-the-us-claims#abstract



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# Renal Function Worsening in Factor-Xa Inhibitors vs Phenprocoumon in Patients with NVAF and Renal Disease

**RELOADED study**

- To investigate the risk of **renal function worsening** by ESRD or dialysis & AKI between riavoroxaban/apixaban and phenprocoumon
- German claim database from 2013 to 2017
- naïve NVAF, overall / CKD 1-4 / CKD 3-4

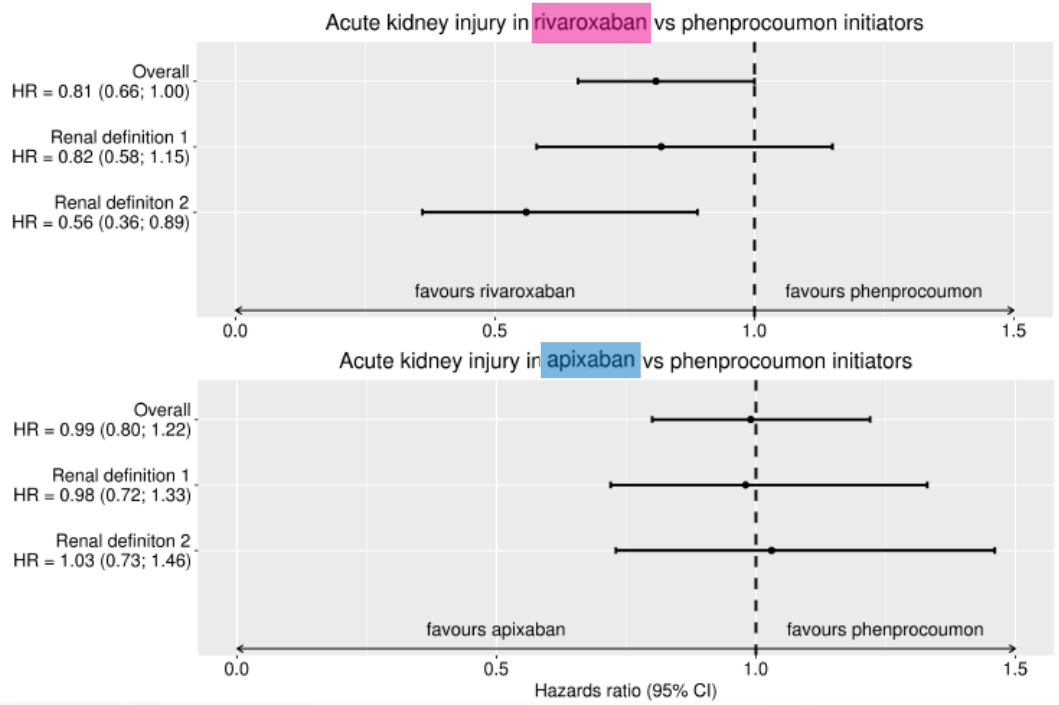
  Definition 1: extended list of ICD-10 (diabetic nephropathy, hypertensive renal disease, chronic renal failure, etc.)

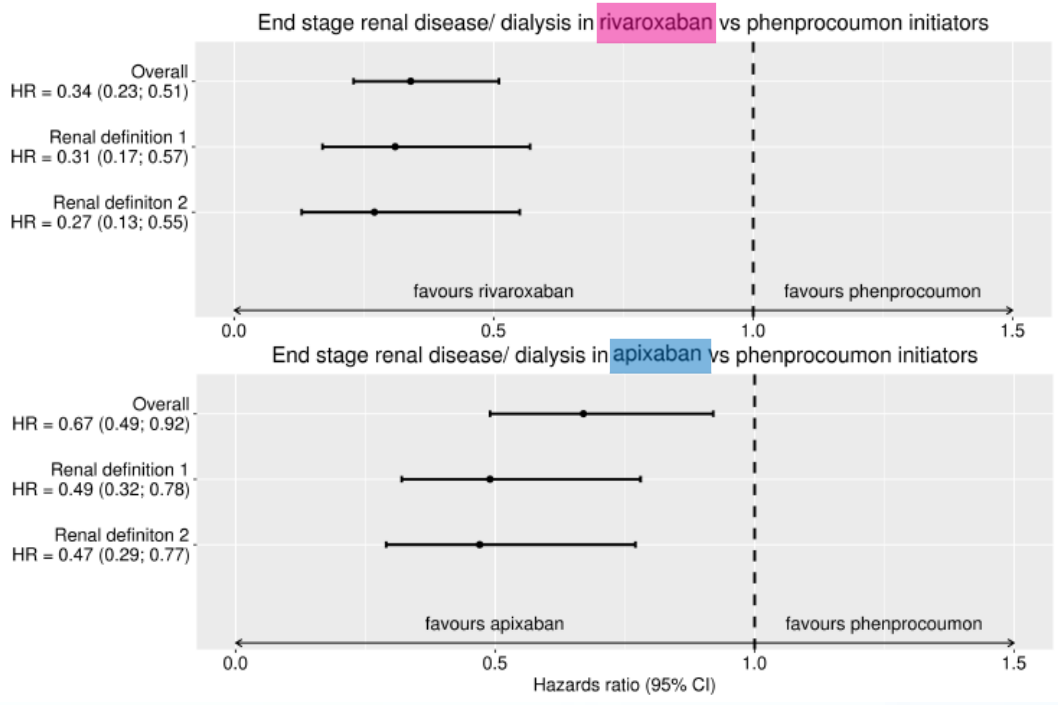
  Definition 2: CKD 3 or 4
- Study outcome:
  - Primary endpoints: AKI, ESRD/dialysis progression risk



Bonnemeier H, Abstract P4749 presented at ESC, Sep 2019; https://esc365.escardio.org/vgn-ext-templating/Congress/ESC-CONGRESS-2019/Poster-Session-5-Atrial-fibrillation-and-oral-anticoagulation-1/199283-renal-function-worsening-in-factor-xa-inhibitors-vs-phenprocoumon-in-patients-with-non-valvular-atrial-fibrillation-and-renal-disease-insights-from-the-reloaded-study#slide

# Rivaroxaban and apixaban reduced renal function worsening to ESRD vs phenprocoumon but only rivaroxaban reduced progression to AKI






Bonnemeier H, Abstract P4749 presented at ESC, Sep 2019; https://esc365.escardio.org/vgn-ext-templating/Congress/ESC-CONGRESS-2019/Poster-Session-5-Atrial-fibrillation-and-oral-anticoagulation-1/199283-renal-function-worsening-in-factor-xa-inhibitors-vs-phenprocoumon-in-patients-with-non-valvular-atrial-fibrillation-and-renal-disease-insights-from-the-reloaded-study#slide

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# Rivaroxaban is further confirmed in real world to be associated with lower risk of adverse renal outcomes than warfarin

| Progression to CKD 5 / ESRD / dialysis | Rivaroxaban | VKA | | | |
|---|---|---|---|---|---|
| | Event rate | | HR | 95% CI | |
| **Yao X et al** [1]<br>Events | N=2,486<br>21 | N=4,185<br>89 | 0.46 | 0.28-0.75 | |
| **RIVAL NVAF** [2]<br>Events / 100 person-years | N=36,318<br>2.67 | N=36,281<br>4.12 | 0.82 | 0.74-0.91 | |
| **CALLIPER** [3]<br>Rivaroxaban 15mg | N=1,466<br>35 | N=5,906<br>248 | 0.53 | 0.35-0.78 | |
| **RELOADED** [4]<br>Rivaroxaban 15mg | N=1,216<br>8 | N=3,531<br>106 | 0.27 | 0.13-0.55 | |

| Acute kidney injury | Rivaroxaban | VKA | | | |
|---|---|---|---|---|---|
| | Event rate | | HR | 95% CI | |
| **Yao X et al** [1]<br>Events | N=2,486<br>145 | N=4,185<br>441 | 0,46 | 0,28-0,75 | |
| **RIVAL NVAF** [2]<br>Events / 100 person-years | N=36,318<br>4.91 | N=36,281<br>8.45 | 0.81 | 0.75-0.87 | |
| **RELOADED** [4]<br>Rivaroxaban 15mg | N=1,216<br>23 | N=3,531<br>104 | 0.56 | 0.36-0.89 | |



1. Yao X et al. *J Am Coll Cardiol.* 2017;70(21):2621–2632
2. Coleman, CI et al. Clinical and Applied Thrombosis/Hemostasis, 2019, Vol 25: 1-8 DOI: 10.1177/1076029619868535
3. Tatsiana Vaitsiakhovich, Craig I. Coleman, Frank Kleinjung, Sebastian Kloss, Burcu Vardar, Simone Werner, Bernhard Schaefer, abstract will be presented in ESC 2019
4. Bonnemeier H et al. Presented at ESOC 2019, Milan, Italy, AS25-066; ClinicalTrials.gov. RELOADED. https://clinicaltrials.gov/ct2/show/NCT03563937 (Accessed May 2019)




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# Rivaroxaban Versus Warfarin in Patients With Nonvalvular Atrial Fibrillation and Severe Kidney Disease or Undergoing Hemodialysis

- To provide real-world data on the relative **safety** and **effectiveness** of rivaroxaban vs. warfarin among patients with CKD 4 or 5 or undergoing dialysis
- Retrospective Truven US MarketScan claims database analysis from 2012 to 2017
- naïve NVAF, CKD 4 or 5 or undergoing hemodialysis
- **Study outcomes**
  - Primary efficacy endpoints: stroke, SE
  - Primary safety endpoints: major bleeding



Coleman, CI et al. Clinical and Applied Thrombosis/Hemostasis, 2019, Vol 25: 1-8 DOI: 10.1177/1076029619868535

# Rivaroxaban Versus Warfarin in Patients With Nonvalvular Atrial Fibrillation and Severe Kidney Disease or Undergoing Hemodialysis

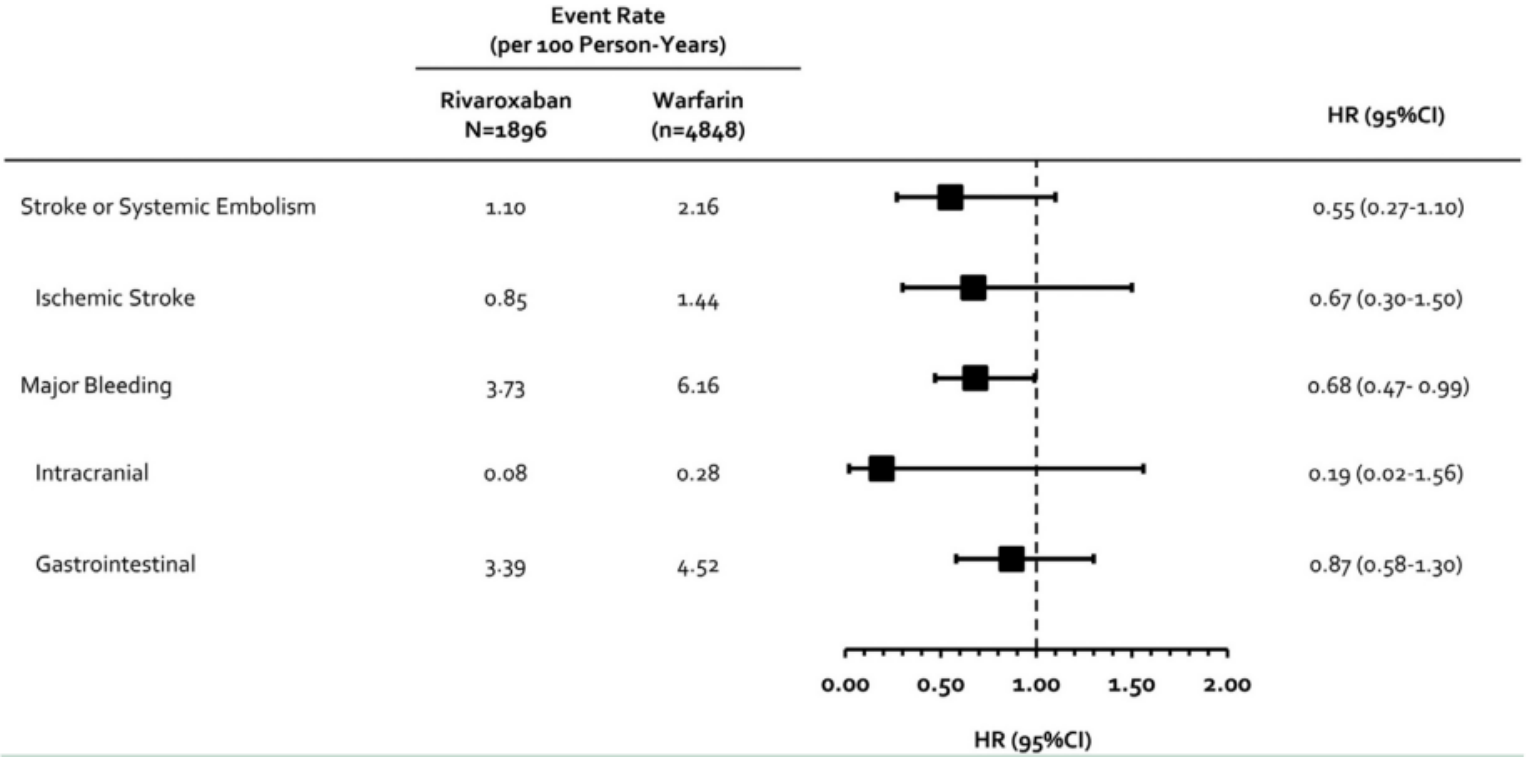


**Figure 1** Event rates and hazard ratios with 95% confidence intervals in inverse probability-of-treatment weighted cohorts of rivaroxaban and warfarin



Coleman, CI et al. *Am J Med*. 2019 May 2. doi: 10.1016/j.amjmed.2019.04.013

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# Take Home Messages

- Rivaroxaban appears associated with lower risks of AKI or progression to stage 5 CKD or need for dialysis versus warfarin in patients with NVAF[1,2,3]
- The reduced dose of rivaroxaban (15mg OD), when used in the routine clinical practice, has appeared to lower significantly the risk of worsening of renal function versus warfarin in NVAF patients with CKD stage 3&4 present at the OAC therapy initiation [3]
- Also, the patients with the co-morbid T2DM holds true for the conclusion as well [3]
- Rivaroxaban appears associated with significantly less major bleeding and similar rates of stroke/SE compared to warfarin in NVAF patients with CKD stage 4 or 5 or underlying hemodialysis. [4]

1. Coleman, CI et al. Clinical and Applied Thrombosis/Hemostasis, 2019, Vol 25: 1-8 DOI: 10.1177/1076029619868535, 2. Bonnemeier H, Abstract P4749 presented at ESC, Sep 2019
3. Vaitsiakhovich T, Abstract P4746 presented at ESC, Sep 2019, 4. Coleman, CI et al. *Am J Med*. 2019 May 2. doi: 10.1016/j.amjmed.2019.04.013



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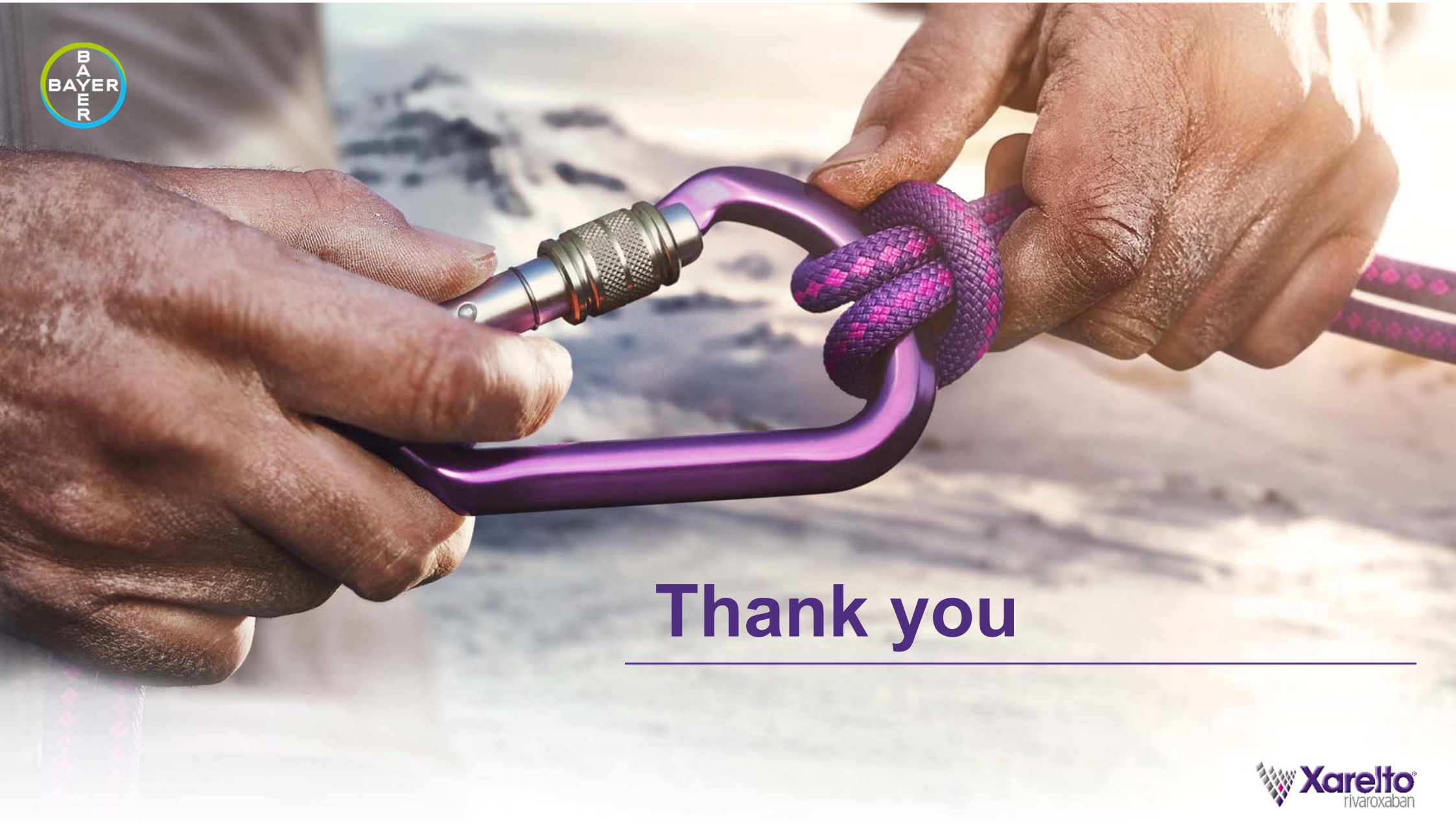
BAYER
Thank you
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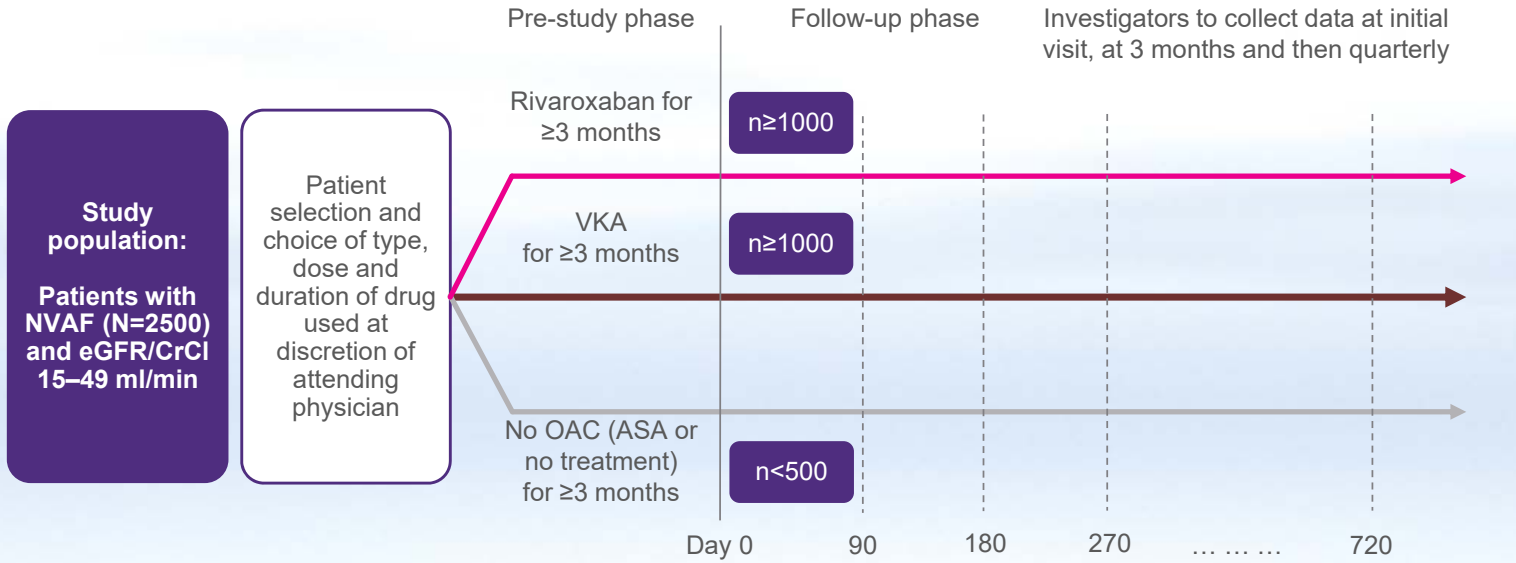
# XARENO – an ongoing real-world study of rivaroxaban in renally impaired patients

- **Official study title:** Factor XA – inhibition in RENal patients with non-valvular atrial fibrillation Observational registry
- **Objective:** To assess CKD progression and safety of anticoagulation strategies in NVAF patients with eGFR 15–49 ml/min /1.73 $m^2$ in routine clinical practice




**Short design**: Observational, open-label, active-controlled, multicentre study (N=2500)



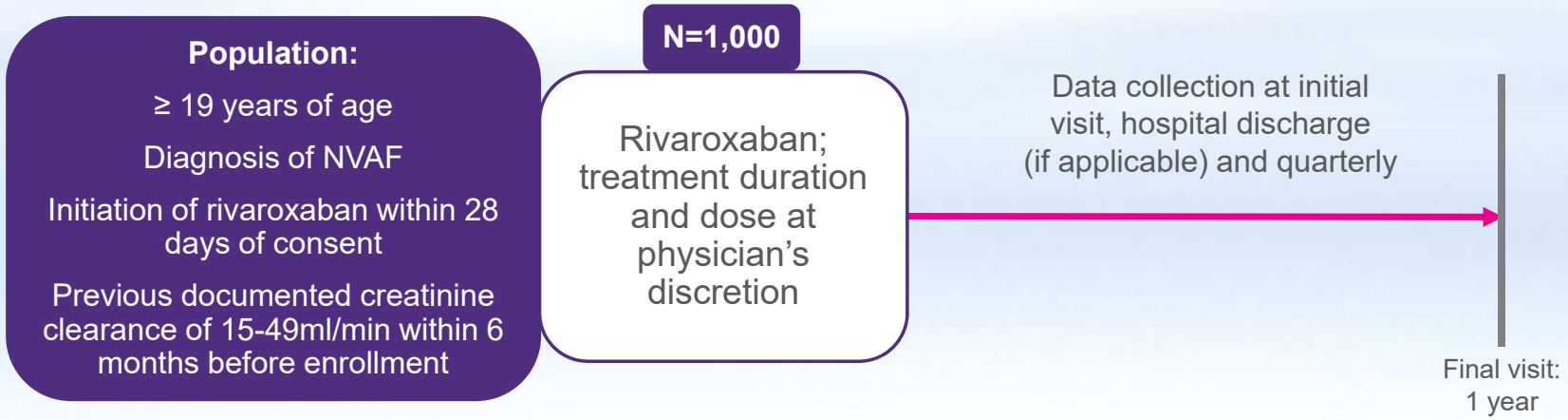
www.clinicaltrials.gov/ct2/show/NCT02663076

# XARENAL- Ongoing Study in Korea

**Official study title: Xarelto® on prevention of stroke and non-central nervous systemic embolism in renally impaired Korean patients with Non-valvular Atrial fibrillation**

**Objective:** To assess safety of rivaroxaban with regard to the incidence proportion of major bleeding in NVAF paitents with moderate to severe renal impairment under routine clinical practice conditions

**Design :** Prospective, multi-centre, non-interventional, observational, single arm cohort study in renally impaired NVAF patients, who are prescribed rivaroxaban to prevent stroke or non-CNS systemic embolism




**Primary outcomes:** Incidence proportion of major bleeding (ISTH definition)

**Secondary outcomes** : Incidence proportion of AE and SAEs, non-major bleeding, symptomatic thrombotic events, all-cause mortality, persistence rate, change in creatinine clearance

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# Real-World Studies Show That Risk of AKI and CKD Is Non-Negligible in Patients with AF Receiving Warfarin or NOACs

- AKI and CKD events identified in retrospective analyses of administrative databases

| Reference | Treatment at baseline | AKI rate (events per year) | HR (95% CI) vs warfarin | |
|---|---|---|---|---|
| | | | AKI* | CKD* |
| Chan *et al*, (N>20,000 [total]) | Warfarin | CKD (6.8–26.0) | | NR |
| | Warfarin | No CKD (2.0–6.2) | | NR |
| | Dabigatran | CKD (2.9–3.95) | 0.62 (0.49–0.77) | NR |
| | Dabigatran | No CKD (1.7–2.6) | 0.56 (0.46–0.69) | NR |
| Yao *et al*, (N=9769) | Warfarin | 10.3 | | |
| | All NOACs | 5.9–9.2 | 0.69–0.84 | 0.46–0.88 |
| Shin *et al*, (N=6412) | Warfarin | 9.49 | | |
| | All NOACs | 7.5 | 0.79 (0.68–0.92) | NR |

These studies did not take into account whether coagulopathy (international normalized ratio 3.0 or significant bleeding) was present when the AKI was identified. *Variously defined (e.g., on-treatment eGFR decline >20–30% per year)

AKI, acute kidney injury; CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; eGFR, estimated glomerular filtration rate; NR, not reported; NOAC, non-vitamin K antagonist oral anticoagulant



Brodsky S *et al*, *J Am Soc Nephrol* 2018;29:2787–2793

# Anticoagulant-Related Nephropathy (ARN) May Be Underdiagnosed in Clinical Practice

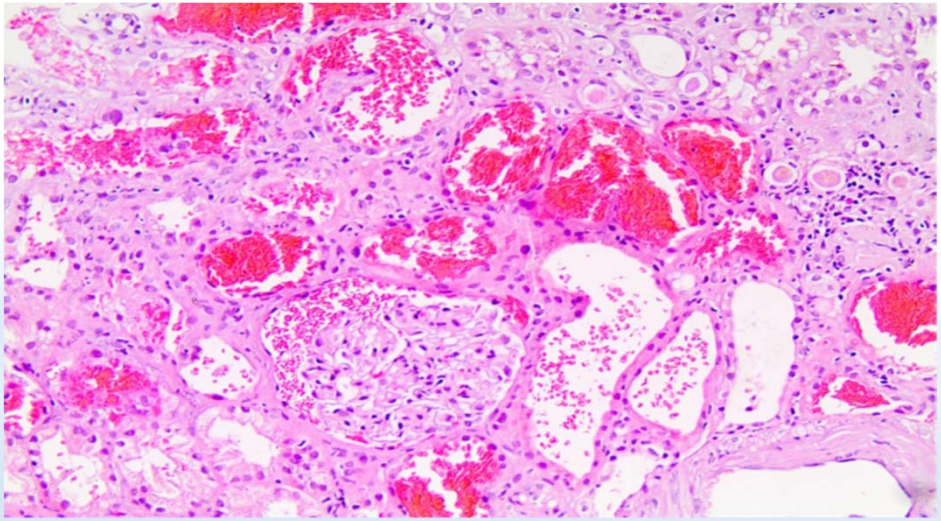
- Presumptive ARN (related to warfarin or a NOAC) occurs mainly in patients who already have multiple risk factors for AKI (e.g., CKD, cardiovascular disease, diabetes or older age)
- It is, therefore, relatively easy to default to an AKI diagnosis of 'multifactorial'
  - ARN is a diagnosis of exclusion unless a kidney biopsy is performed
- Nephrologists are naturally cautious regarding kidney biopsy in patients who require anticoagulant therapy, although biopsy in such patients is an established procedure



Brodsky S *et al*, *J Am Soc Nephrol* 2018;29:2787–2793

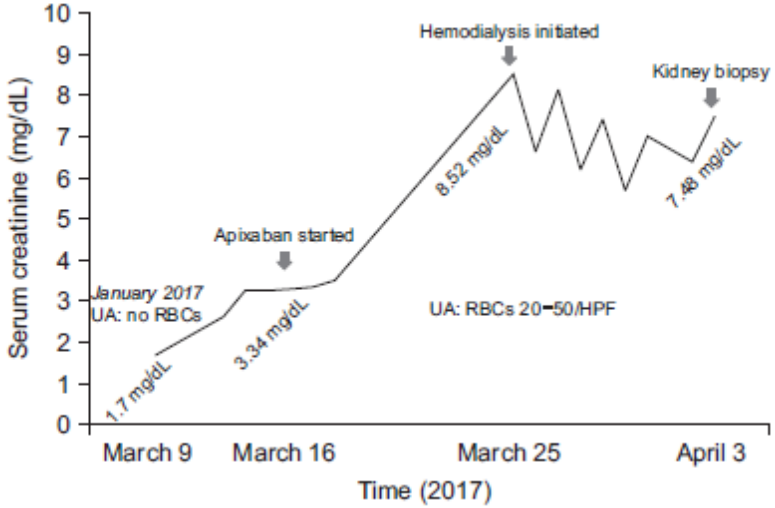
# Patients Treated with NOACs May Be at Risk of Anticoagulant-Related Nephropathy

## Case of ARN with dabigatran[1]



- Occlusion of tubular lumens by RBC casts in a 78-year-old patient receiving dabigatran 110 mg bid

## Case of ARN with apixaban[2]




- Serum creatinine changes in association with apixaban treatment in an 82-year-old patient

Further research is needed to elucidate the pathogenesis of ARN and identify risk factors[1]

ARN, anticoagulant-related nephropathy; bid, twice daily; NOAC, non-vitamin K antagonist oral anticoagulant; RBC, red blood cell



Kalaitzidis RG *et al*, *Int Urol Nephrol* 2017;49:1401–1407; 2. Brodsky SV *et al*, *Kidney Res Clin Pract* 2017;39:387–392

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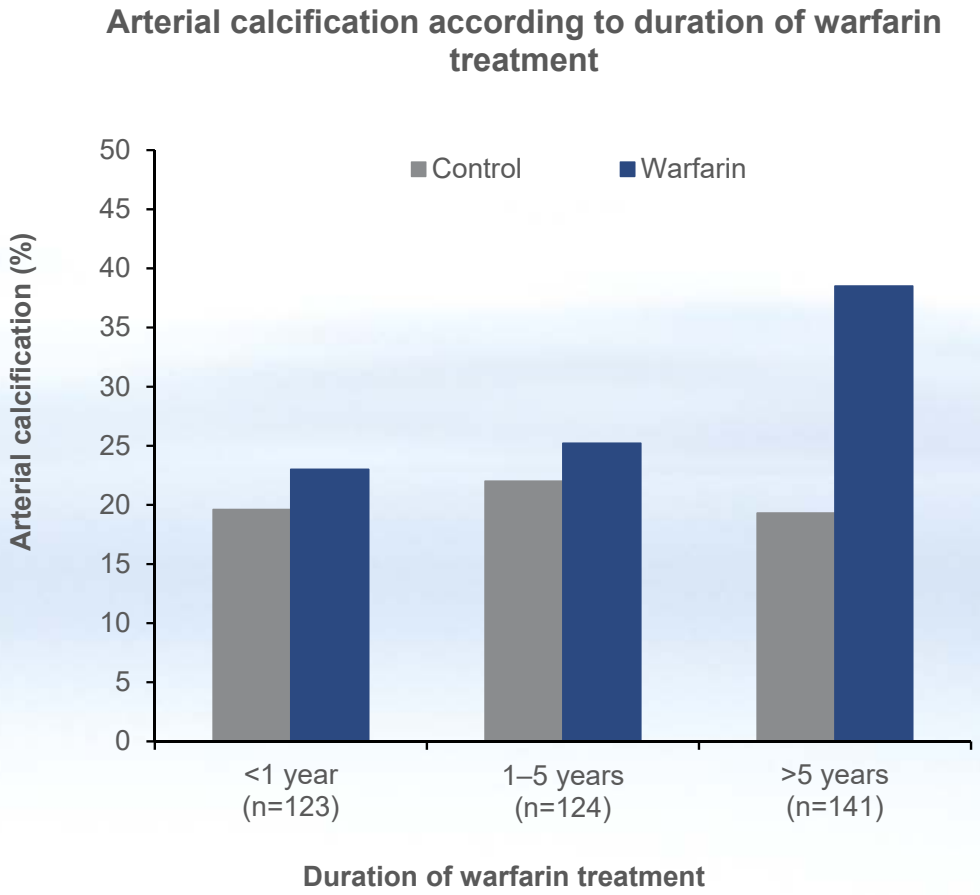
# Worsening Renal Function May Be Exacerbated by Use of Warfarin

- Retrospective, matched, cohort study in 430 warfarin users and 430 patients without warfarin exposure (mean age 67 years in both groups)
- Matched for age, sex and diabetes status
  - Patients with end-stage renal disease or serum creatinine >2 mg/dl were excluded
- Calcification analysis: X-rays of lower-extremity arteries at knee level and below






Han KH *et al*, *J Am Heart Assoc* 2016;5:e002665

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