Clinical Study Synopsis

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1. Abstract

Acronym/Title	Evaluation of Clinical outcomes among non-valvular Atrial fibriLLatIon PatiEnts with Renal dysfunction treated with warfarin or reduced dose rivaroxaban (CALLIPER)
Report version and date **Author**	v 1.0, 31 JUL 2019 [redacted]
Keywords	NVAF, Rivaroxaban, Renal dysfunction, Effectiveness, Safety
Rationale and background	Renal impairment is a common comorbidity in patients with non-valvular atrial fibrillation (NVAF); it increases both the risk of stroke and the risk of bleeding during the established oral anticoagulant treatment with either vitamin K antagonists or non-VKA oral anticoagulants (NOAC). For NVAF patients with higher degree of renal insufficiency, reduced dosing regimen of NOACs is required. Clinical and "real world" data on treatment outcomes in these patients are scarce. This study was conducted to examine the effectiveness and safety of the reduced dose rivaroxaban (15 mg once daily (OD)) as compared to warfarin in patients with NVAF and renal dysfunction in routine clinical practice.
Research question and objectives	The objective of the study was to evaluate the risk of ischemic stroke (IS), intracranial hemorrhage (ICH) (individually and as a composite endpoint), bleeding-related hospitalization, and progression to stage 5 chronic kidney disease (CKD), kidney failure or need for dialysis, in NVAF patients with renal dysfunction treated with the reduced dose rivaroxaban (15 mg OD) compared to warfarin in routine clinical practice.
Study design	A retrospective cohort study using the IBM Watson MarketScan Commercial Claims and Medicare Supplemental Databases was conducted.

Setting	The source population of this study included all insured individuals in the IBM Watson MarketScan databases. IBM Watson MarketScan claims data between 1 JAN 2012 and 30 SEP 2017 were used for the study.
Subjects and study size, including dropouts	The NVAF patients with renal dysfunction and a claim for warfarin or rivaroxaban were identified in the IBM Watson MarketScan databases and divided into 4 cohorts (according to two different lists of International Classification of Diseases codes for renal conditions and inclusion or exclusion of cancer as comorbidity) and 4 subcohorts (sub-group of each cohort with type 2 diabetes mellitus (T2DM)). After applying all of the defined selection criteria, there were 7,368 patients in the Cohort 1(NVAF + CKD 3/4 and cancer included); 5,426 patients in the Cohort 2 (NVAF + CKD 3/4 and cancer excluded); 15,975 patients in the Cohort 3 (NVAF + renal extended and cancer included); and 11,705 patients in the Cohort 4 (NVAF + renal extended and cancer excluded). There were 3,905 patients in the Subcohort 1 (NVAF + CKD 3/4 + T2DM and cancer included), 2,919 patients in the Subcohort 2 (NVAF + CKD 3/4 + T2DM and cancer excluded); 7,860 patients in the Subcohort 3 (NVAF + renal extended + T2DM and cancer included); and 5,913 patients in the Subcohort 4 (NVAF + renal extended + T2DM and cancer excluded).
Variables and data sources	Patients' baseline characteristics such as age, gender, comorbidities, and comedications were collected at the index date. The outcomes of interest were IS, ICH (individually and as a composite endpoint), bleeding-related hospitalization events, and progression to stage 5 CKD, kidney failure or need for dialysis. Baseline characteristics and outcome events were assessed using diagnoses, procedures, as well as drug codes. Bleeding-related hospitalizations were identified using the Cunningham algorithm. IBM Watson MarketScan databases that capture longitudinal, individual-level administrative claims data of the United States (US) population were utilized for this study. Because of the large numbers of patients in these databases, it is possible to assess the effectiveness and safety of medications of interest, or to compare different medications.

Results	The risk of IS, ICH, IS or ICH (composite endpoint), bleeding-related hospitalization, and progression to CKD stage 5/kidney failure/dialysis was evaluated for 4 cohorts (patients with CKD 3/4 or renal extended + inclusion or exclusion of cancer as comorbidity) and the subgroups (with T2DM) of each cohort. The patients were followed until the occurrence of outcome, start of an additional exposure, discontinuation of the exposure, insurance disenrollment or end of data availability. ***Cohort 1 (NVAF + CKD 3/4 and cancer included)*** After applying all the defined selection criteria, 5,903 and 1,465 naïve patients were selected in warfarin and rivaroxaban exposure groups, respectively. After propensity score-based (PS-based) *1:1* matched analysis, 1,460 patients were available in both the exposure groups. After PS-based *1:n* matched analysis, 5,124 and 1,367 patients were available for IS, ICH, IS, or ICH (composite) and bleeding-related hospitalization outcomes whereas 2,881 and 1,458 patients were available for progression to CKD stage 5/kidney failure/dialysis outcome, in warfarin and rivaroxaban exposure groups, respectively. Baseline covariates were well balanced after matching (absolute standardized differences ≤0.1 for all covariates). Overall, rivaroxaban (reduced dose 15 mg OD) was associated with a significant risk reduction of progression to CKD stage 5/kidney failure/dialysis by inverse probability of treatment weighting (IPTW) analysis (47%; p-value <0.01). The results were similar by sensitivity analyses; based on several analytical approaches the risk reduction was estimated to be at least 38% (p-values ≤0.01) in comparison to warfarin. By IPTW analysis, the risk reduction of IS (23%) and IS or ICH (39%) was more pronounced with rivaroxaban in comparison to warfarin; however, did not reach statistical significance. The results were similar by sensitivity analyses; the risk reduction was estimated to be at least 13% for IS and 29% for IS or ICH in comparison to warfarin (based on several analytical approaches). The risk of bleeding-related hospitalization events with rivaroxaban versus warfarin, although numerically higher (14%) by IPTW analysis, was of no statistical significance. The results were similar by sensitivity analyses; the risk of bleeding-related hospitalization events with rivaroxaban as compared to warfarin was not higher than 31% (based on several analytical approaches).

	Cohort 2 (NVAF + CKD 3/4 and cancer excluded)
	After applying all the defined selection criteria, 4,346 and 1,080 naïve patients were selected in warfarin and rivaroxaban exposure groups, respectively. After PS-based matching by *1:1* matched analysis, 1,078 patients were available in both the exposure groups. After PS-based *1:n* matched analysis, 3,775 and 993 patients were available for IS, ICH, IS, or ICH (composite) and bleeding-related hospitalization outcomes whereas 2,133 and 1,075 patients were available for progression to CKD stage 5/kidney failure/dialysis outcome, in warfarin and rivaroxaban exposure groups, respectively. Baseline covariates were well balanced after matching (absolute standardized differences ≤0.1 for all covariates).
	Overall, rivaroxaban (reduced dose 15 mg OD) was associated with a significant risk reduction of progression to CKD stage 5/kidney failure/dialysis by IPTW (36%; p-value 0.04), and *1:1* matched analyses (48%; p-values <0.01) in comparison to warfarin. The risk reduction by all confounders adjusted and *1:n* matched analyses was in favor of rivaroxaban (30% and 31%, respectively), but did not reach statistical significance.
	By IPTW analysis, the risk reduction of IS (22%) and IS or ICH (38%) was more pronounced with rivaroxaban in comparison to warfarin but did not reach statistical significance. The results were generally similar by sensitivity analyses; the risk reduction was at least 27% for IS or ICH and 15% for IS in comparison to warfarin (based on several analytical approaches), except by *1:n* matched analysis for IS.
	The risk of bleeding-related hospitalization events with rivaroxaban although higher (40%) in comparison to warfarin was of no statistical significance by IPTW analysis. The results were similar by sensitivity analyses; the risk of bleeding-related hospitalization events with rivaroxaban as compared to warfarin was not higher than 45% (based on several analytical approaches).
	Cohort 3 (NVAF + renal extended and cancer included)
	After applying all the defined selection criteria, 13,268 and 2,707 naïve patients were selected in warfarin and rivaroxaban exposure groups, respectively. After PS-based matching by *1:1* matched analysis, 2,706 patients were available in both the exposure groups. After PS-based *1:n* matched analysis, 10,317 and 2,587 patients were available for IS, ICH, IS, or ICH (composite) and bleeding-related

	hospitalization outcomes whereas 5,315 and 2,681 patients were available for progression to CKD stage 5/kidney failure/dialysis outcome, in warfarin and rivaroxaban exposure groups, respectively. Baseline covariates were well balanced after matching (absolute standardized differences ≤0.1 for all covariates). Overall, rivaroxaban (reduced dose 15 mg OD) was associated with a risk reduction of progression to CKD stage 5/kidney failure/dialysis (24%) by IPTW analysis versus warfarin; however, did not reach statistical significance. The results were similar by sensitivity analyses and the risk reduction with rivaroxaban was at least 19% in comparison to warfarin (based on several analytical approaches), except by *1:1* matched analysis (33%; p-value: 0.03). By IPTW analysis, rivaroxaban (reduced dose 15 mg OD) was associated with a significant risk reduction of ICH (66%, p-value: 0.04) in comparison to warfarin. The risk reduction of IS (6%) and composite endpoint (IS or ICH) (32%) by IPTW analysis was more pronounced with rivaroxaban but did not reach statistical significance. By sensitivity analyses, the risk reduction was at least 51% for ICH, 26% for IS or ICH and 9% for IS in comparison to warfarin (based on several analytical approaches), however, did not reach statistical significance. The risk of bleeding-related hospitalization events with rivaroxaban versus warfarin, although numerically higher by IPTW (22%) analysis, was of no statistical significance. The results were similar by sensitivity analyses and the risk of bleeding-related hospitalization events with rivaroxaban as compared to warfarin was not higher than 26% (based on several analytical approaches). ***Cohort 4 (NVAF + renal extended and cancer excluded)*** After applying all the defined selection criteria, 9,737 and 1,968 naïve patients were selected in warfarin and rivaroxaban exposure groups, respectively. After PS-based matching by *1:1* matched analysis, 1,965 patients were available in both the exposure groups. After PS-based *1:n* matched analysis, 7,410 and 1,873 patients were available for IS, ICH, IS, or ICH (composite) and bleeding-related hospitalization outcomes whereas 3,878 and 1,951 patients were available for progression to CKD stage 5/kidney failure/dialysis outcome in warfarin and rivaroxaban exposure groups, respectively. Baseline covariates were

	well balanced after matching (absolute standardized differences ≤0.1 for all covariates). Overall, rivaroxaban (reduced dose 15 mg OD) was associated with a risk reduction of progression to CKD stage 5/kidney failure/dialysis by IPTW analysis (26%) in comparison to warfarin but did not reach statistical significance. The results were generally similar by sensitivity analyses; the risk reduction of progression to CKD stage 5/kidney failure/dialysis was at least 17% in comparison to warfarin (based on several analytical approaches), except 1:1 matched analysis. By IPTW analysis, the risk reduction of IS (40%) and IS or ICH (47%) was more pronounced with rivaroxaban in comparison to warfarin, however, did not reach statistical significance. The results were similar by sensitivity analyses; the risk reduction was at least 39% for IS or ICH and 26% for IS in comparison to warfarin (based on several analytical approaches). The risk of bleeding-related hospitalization events with rivaroxaban although numerically higher (26%) in comparison to warfarin, was of no statistical significance by the main IPTW analysis. The results were similar by sensitivity analysis; the risk of bleeding-related hospitalization events with rivaroxaban as compared to warfarin was not higher than 48% (based on several analytical approaches). ***Subcohort 1 (NVAF + CKD 3/4 + T2DM and cancer included)*** In Subcohort 1 (total 3,905 naïve patients: 3,159 and 746 in warfarin and rivaroxaban exposure groups, respectively), rivaroxaban (reduced dose 15 mg OD) was associated with a significant risk reduction of progression to CKD stage 5/kidney failure/dialysis by IPTW (50%; p-value <0.01) analysis. The results were similar by sensitivity analyses; the risk reduction of progression to CKD stage 5/kidney failure/dialysis was at least 38% (p-values ≤0.05) in comparison to warfarin (based on several analytical approaches). ***Subcohort 2 (NVAF + CKD 3/4 + T2DM and cancer excluded)*** In Subcohort 2 (total 2,919 naïve patients: 2,368 and 551 in warfarin and rivaroxaban exposure groups, respectively), rivaroxaban (reduced dose 15 mg OD) was associated with a risk reduction of progression to CKD stage 5/kidney failure/dialysis by IPTW analysis (27%) in comparison to

	warfarin but did not reach statistical significance. The results were similar by sensitivity analyses; the risk reduction of progression to CKD stage 5/kidney failure/dialysis was at least 35% in comparison to warfarin (based on several analytical approaches), and by 1:1 matched analysis reached statistically significant 46%, with p-value: 0.04. ***Subcohort 3 (NVAF + renal extended + T2DM and cancer included)*** In Subcohort 3 (total 7,860 naïve patients: 6,548 and 1,312 in warfarin and rivaroxaban exposure groups, respectively), rivaroxaban (reduced dose 15 mg OD) was associated with a risk reduction of progression to CKD stage 5/kidney failure/dialysis by IPTW analysis (27%) in comparison to warfarin but did not reach statistical significance. The results were generally similar by sensitivity analyses and the risk reduction of progression to CKD stage 5/kidney failure/dialysis was at least 21% in comparison to warfarin (based on several analytical approaches). ***Subcohort 4 (NVAF + renal extended + T2DM and cancer excluded)*** In Subcohort 4 (total 5,913 naïve patients: 4,944 and 969 in warfarin and rivaroxaban exposure groups, respectively), rivaroxaban (reduced dose 15 mg OD) was associated with a risk reduction of progression to CKD stage 5/kidney failure/dialysis by IPTW analysis (28%) in comparison to warfarin but did not reach statistical significance. The results were generally similar by sensitivity analyses and the risk reduction of progression to CKD stage 5/kidney failure/dialysis was at least 20% in comparison to warfarin (based on several analytical approaches).
Discussion	The current analyses by all methods (IPTW and sensitivity analyses) demonstrated that the reduced dose of rivaroxaban was associated with significantly lower risk of progression to CKD stage 5/kidney failure/dialysis in NVAF patients with CKD stage 3 and 4, when compared to warfarin. In the NVAF patients with CKD stage 3 and 4 who had T2DM as comorbidity, the use of rivaroxaban over warfarin was associated with a significantly reduced risk of worsening of renal function. Moreover, when compared by PS-based *1:1* matched analysis; the risk rate of progression to CKD stage 5/kidney failure/dialysis per 1,000 person-years was approximately 1.5 folds higher with warfarin over rivaroxaban. This signifies the potential of warfarin in compromising the renal function, and at the same time

	demonstrates the effectiveness of rivaroxaban in preserving the renal function, in the studied population. In NVAF patients who had renal dysfunction defined by the renal extended approach (CKD stage 3/ 4 or other kidney disease such as cystic kidney disease, unspecified kidney failure, chronic or unspecified nephritic syndrome, nephrotic syndrome, recurrent and persistent hematuria, nephropathy (diabetic, hypertensive, hereditary), and chronic tubulointerstitial nephritis) rivaroxaban (reduced dose 15 mg OD) was generally associated with lower risk of progression to CKD stage 5/kidney failure/dialysis versus warfarin, as observed by IPTW and sensitivity analyses, although the results were not statistically significant. These findings were also observed in the NVAF patients with renal dysfunction defined by renal extended approach, who additionally had T2DM as comorbidity. The risk reduction of IS, and IS or ICH (composite outcome) was generally found to be more pronounced with rivaroxaban in comparison to warfarin, as observed by IPTW and sensitivity analyses in NVAF patients with CKD stage 3 and 4. The risk reduction of IS and IS or ICH (composite outcome) was generally found to be more pronounced with rivaroxaban in comparison to warfarin, as observed by sensitivity analyses in NVAF patients with renal disfunction (identified by renal extended approach) and T2DM. The risk reduction of the bleeding-related hospitalization events with rivaroxaban was generally comparable to warfarin as evident by IPTW and sensitivity analyses. In summary, various analytical approaches were applied in this study. Besides IPTW analysis and classical fully adjusted analysis, the treatment groups in each cohort and subcohort were matched by applying PS matching that minimized confounding caused by observed baseline covariates. Generalizability of the results of this study in the US population should be considered acceptable as individuals enrolled in the MarketScan databases are largely representative of the US population in terms of age, sex, and type of health insurance coverage. However, as the MarketScan databases largely cover employees and their dependents, patients with conditions that prevent them to be employed might be underrepresented. Additionally, this study successfully identified the NVAF patients with renal dysfunction (algorithms using ICD

	codes) in the MarketScan databases without involving laboratory measures. The strategy may be useful for future RWE studies involving various data sources. ***Conclusion*** The overall results suggest that reduced dose of rivaroxaban is safe and effective over warfarin in a large population of NVAF patients with renal dysfunction (with and without T2DM). Rivaroxaban appears effective in preserving the renal function (progression to CKD stage 5/kidney failure/dialysis) when used in these NVAF patients. The risk reduction of the bleeding-related hospitalization with rivaroxaban is generally comparable to warfarin.
Marketing Authorization Holder(s)	Bayer AG, 51368 Leverkusen, Germany
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