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Incidence and characteristics of major bleeding among rivaroxaban users with renal disease and nonvalvular atrial fibrillation

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Objective Patients with nonvalvular atrial fibrillation (AF) and renal disease (RD) who receive anticoagulation therapy appear to be at greater risk of major bleeding (MB) than AF patients without RD. As observed in past studies, anticoagulants are frequently withheld from AF patients with RD due to concerns regarding bleeding. The objective of this study was to evaluate the incidence and pattern of MB in those with RD, as compared to those without RD, in a population of rivaroxaban users with nonvalvular AF.

Methods Electronic medical records of over 10 million patients from the Department of Defense Military Health System were queried to identify rivaroxaban users with nonvalvular AF. A validated algorithm was used to identify MB-related hospitalizations. RD was defined through diagnostic codes present within 6 months prior to the bleeding date for MB cases and end of study participation for non-MB patients. Data were collected on patient characteristics, comorbidities, MB management, and outcomes.

Results Overall, 44,793 rivaroxaban users with nonvalvular AF were identified. RD was present among 6,921 patients (15.5%). Patients with RD had a higher rate of MB than those without RD, 4.52 per 100 person-years versus 2.54 per 100 person-years, respectively. The fatal bleeding outcome rate (0.09 per 100 person-years) was identical between those with and without RD.

Conclusion In this post-marketing study of 44,793 rivaroxaban users with nonvalvular AF, RD patients experienced a higher MB rate than those without RD. The higher rate of MB among those with RD may be due to the confounding effects of comorbidities.

Keywords Atrial fibrillation; Major bleeding; Rivaroxaban; Renal disease

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Capsule Summary

What is already known

Patients with nonvalvular atrial fibrillation (AF) and renal disease (RD) who receive anticoagulation therapy appear to be at greater risk of major bleeding (MB) than AF patients without RD. As observed in past studies, anticoagulants are frequently withheld from AF patients with RD due to concerns regarding bleeding.

What is new in the current study

In this post-marketing safety study of 44,793 rivaroxaban users with nonvalvular AF, those with RD experienced a higher rate of MB than those without RD, similar to the findings from the clinical trial of rivaroxaban. Between the MB cohorts with and without RD, the fatal bleeding outcome rate was identical and the clinical management of MB cases was similar. The higher rate of MB found in this study among those with RD may be due to the confounding effects of comorbidities, as those with RD had a higher prevalence of comorbidities compared to those without RD.

INTRODUCTION

Atrial fibrillation (AF) is a common arrhythmia, and prevalence increases with age.[1] The most devastating and potentially fatal consequence of AF is ischemic stroke.[2] It is estimated that up to 15% of those with AF have some degree of renal disease (RD).[2] For those with renal dysfunction and AF, treatment planning can be problematic since this population is at increased risk for both thromboembolic events and bleeding related to anticoagulation therapy.[3-6] Nonetheless, all patients with AF should be evaluated for stroke risk and placed on long-term anticoagulation therapy for stroke prevention.[1,2,7]

Rivaroxaban is a direct oral anti-coagulant (DOAC) with a rapid onset of administration, and is partially eliminated by the kidneys.[1,7] Fox et al.[3] showed that patients taking warfarin or rivaroxaban who also had AF and moderate renal insufficiency experienced higher incidence of stroke and bleeding than those with normal renal function. Patients on rivaroxaban who had renal impairment showed comparable bleeding rates to patients on warfarin but with less critical organ bleeding and fatal bleeding,[3] though rivaroxaban increases the risk of gastrointestinal (GI) bleeding when compared with warfarin.[8]

In past studies, it has been observed that anticoagulation therapy is frequently withheld from patients with both AF and renal dysfunction due to concerns regarding bleeding,[9] and real-world studies regarding oral anticoagulation therapy in patients with renal dysfunction are limited. To better understand the safety profile of rivaroxaban in this context, we examined the incidence of major bleeding (MB) by RD status in a diverse population of rivaroxaban users with nonvalvular AF. This evaluation was derived from an ongoing, 5-year pharmacovigilance study, designed to provide longitudinal safety data by actively obtaining information associated with MB among rivaroxaban users in the post-approval setting.

METHODS

Data source and patient population

This retrospective observational study utilized the US Department of Defense (DoD) healthcare database. The DoD Military Health System (MHS) covers active and retired military service members and their families, and has one of the largest electronic healthcare systems in the US, with nearly 10 million active beneficiaries.[10] The MHS is not linked with data from the Veterans Affairs (VA); the MHS and the VA are separate entities and provide care through healthcare systems predominantly exclusive of one another, therefore this study does not contain data from the VA patient population.

The proportion of patients 65 years of age and older within the MHS is 20%,[11] compared to 13% of the US population.[12] A broader representation of elderly patients in the MHS allows more comprehensive study of conditions prevalent in older age. The MHS contains longitudinal, electronic medical records (EMRs) that are continually updated and comprised of administrative, medical, pharmacy, and clinical data.

The patients in this study are insured through the MHS, though they are not required to use military medical facilities for care. Many patients use TRICARE, the insurance arm of the DoD, to obtain care in non-military (civilian) facilities. Regardless of where care takes place, all claims and related clinical information for each encounter are captured in the DoD MHS databases.

Study interval and patient eligibility

The observational period for this study was January 1, 2013 to June 30, 2015, and only patients with nonvalvular AF diagnoses who were taking rivaroxaban were included. The data analyzed for the study cohort were identified via relevant International Classification of Diseases, 9th revision, clinical modification (ICD-

Table 1. Nonvalvular atrial fibrillation renal disease patients by diagnosis code

Diagnosis code	Diagnosis description	Patients[a]
580.x	Acute glomerulonephritis	6 (0.1)
581.x	Nephrotic syndrome	34 (0.5)
582.x	Chronic glomerulonephritis	19 (0.3)
583.x	Nephritis and nephropathy	219 (3.2)
584.x	Acute kidney failure	2,212 (32.0)
585.x	Chronic kidney disease	5,767 (83.3)
586	Renal failure, unspecified	515 (7.4)
587	Renal sclerosis, unspecified	55 (0.8)
792.5	Cloudy dialysis effluent	2 (0)
V42.0	Kidney replaced by transplant	41 (0.6)
V45.1x	Postsurgical renal dialysis status	66 (1.0)
V56.x	Dialysis and catheter care	32 (0.5)

Values are presented as number (%).
[a]Patients can count toward more than one renal disease diagnosis code.

9-CM) diagnosis and procedure codes and Common Procedure Terminology (CPT)/Healthcare Common Procedure Coding System (HCPCS) procedure codes listed in any available procedure field within any medical encounter record. The nonvalvular AF definition was based on one or more medical encounters with an AF diagnosis, plus the absence of exclusionary valvular criteria. All patients meeting the definition for nonvalvular AF were included in the study, regardless of incident or prevalent rivaroxaban usage, as long as the patient was identified as having nonvalvular AF prior to or concurrent with rivaroxaban usage.

Data were collected on patients with and without RD. Renal disease (reflective of impaired renal function) was defined through the presence of one or more diagnostic codes (Table 1) within 6 months prior to the bleeding date for MB cases and end of study participation for non-MB patients.

Outcome of interest

The primary outcome of interest was MB, as defined by the Cunningham algorithm,[13] a validated method that uses administrative data for identification of MB events that result in a hospitalization. This algorithm employs a systematic approach to identify MB events from a primary discharge diagnosis using ICD-9-CM diagnosis and ICD-9-CM/CPT procedure codes. The types of MB events considered were differentiated by the following bleeding sites: gastrointestinal bleeding, hemorrhagic strokes, other intracranial bleeds, genitourinary bleeding, and bleeding at other sites. The use of bleeding diagnoses showed a positive predictive value of 89% to 99% in Cunningham's validation study, and this algorithm has been used in other clinical studies to identify serious bleeding events.[14-19]

MB events were included if they occurred during rivaroxaban exposure plus 7 days post-discontinuation. Patients were evaluated for MB throughout the study period until censored at the earliest occurrence of any one of four events: a MB event, death, loss of MHS eligibility, or end of the study interval.

Demographic and baseline characteristic data were collected on all participants. Data regarding specific comorbid conditions were also collected, including hypertension, cardiovascular conditions, and history of bleeding, among others. CHA_2SD_2-VASc scores[20] were calculated for each patient. Dose at time of bleeding was captured, as was length of rivaroxaban exposure, using prescription dispensing information from the date of therapy initiation until its discontinuation.

For patients who experienced a MB event, additional data were collected on MB management and fatal outcomes. A fatal outcome was defined as death occurring during the MB-related hospitalization. The incidence of MB, related characteristics, and fatal outcomes were stratified by RD status (yes/no).

Statistical analyses

Descriptive statistics were calculated using SAS ver. 9.4 (SAS Institute, Cary, NC, USA) to evaluate characteristics of the study population. Baseline characteristics of patients were reported as mean values ± standard deviation for continuous variables. Categorical variables were summarized using counts and proportions. No hypothesis testing was planned or performed.

The incidence rates for MB and fatal outcomes were calculated using a person-time approach: the number of patients with a first episode of MB divided by the rivaroxaban exposure time-at-risk, presented per 100 person-years. Incidence rates are presented with 95% confidence intervals (CIs).

Funding source and human subjects protections

This post-marketing safety surveillance study was funded by Janssen Scientific Affairs, LLC and Bayer HealthCare. Health ResearchTx LLC conducted the analyses. The research data were derived from an approved Naval Medical Center, Portsmouth, VA institutional review board protocol (NMCP.2013.0021) and the research was conducted in compliance with federal and state laws, including HIPAA (Health Insurance Portability and Accountability Act) of 1996. The reviewing institutional review board granted a waiver of consent and all patient data were fully anonymized to ensure adherence to the Privacy Rule and to safeguard patient confidentiality.

RESULTS

The study population included 44,793 rivaroxaban users with nonvalvular AF, of which 6,921 (15.5%) had RD. As shown in Table 1,

the predominant RD diagnosis was chronic kidney disease (83.3% of patients) followed by acute kidney failure (32.0%). Among those who experienced a MB event, the mean age was nearly the same between those with and without RD, 78.3 versus 78.8 years (Table 2).[21] In patients who experienced a MB event, 60.3% of the RD patients were male, compared to 48.7% in the non-RD cohort. The RD cohort generally had higher prevalence of comorbidities than those without RD (Table 2),[21] with hypertension and coronary heart disease being most common across the entire study cohort. The higher prevalence of comorbidities in the RD cohort is also evident in the CHA_2DS_2-VASc score, with a mean (standard deviation) score among MB patients with RD of 5.1 (1.4), compared to 4.4 (1.5) among MB patients without RD.

In the RD cohort, the most common dose among those with MB was 15 mg (51.6%) followed by 20 mg (44.6%). A similar distribution was also seen in the RD group that did not experience MB, though the 20-mg dosage group was slightly higher than the 15-mg group, 50.3% and 43.5%, respectively. Comparatively,

Table 2. Baseline patient characteristics of nonvalvular atrial fibrillation rivaroxaban users with and without renal disease, by MB status

Characteristics	Renal disease		No renal disease	
	MB patients (n = 312)	Patients without MB (n = 6,609)	MB patients (n = 981)	Patients without MB (n = 36,891)
Age (yr)[a]	78.3 ± 7.7	78.5 ± 8.3	78.8 ± 7.9	75.8 ± 10.3
Sex, male	60.3	59.0	48.7	55.6
Comorbid[b] condition				
Hemophilia	0	0	0	0
History of hospitalization for bleeding	2.2	0.8	1.2	0.1
Ulcer	3.8	1.8	2.5	0.7
History of seizures	2.9	2.7	2.2	1.3
Diagnosed dementia	7.1	11.9	9.3	5.3
Hepatic disease	15.4	10.7	5.5	3.8
Prior ischemic stroke	10.3	7.6	6.6	3.4
Heart failure	53.5	45.3	32.7	15.7
Previous cerebrovascular event	31.4	22.9	24.5	11.3
Hypertension	95.2	91.3	84.9	62.3
Diabetes mellitus	53.2	47.8	31.2	22.8
Coronary heart disease	62.2	51.0	48.0	27.2
Venous thromboembolism	11.2	9.5	7.3	4.0
Malignancy	22.1	22.3	19.6	14.8
CHA_2DS_2-VASc scores	5.1 ± 1.4	4.7 ± 1.6	4.4 ± 1.5	3.3 ± 1.6
0	0	0.2	0.2	2.8
1	0	0.9	1.9	8.2
2	1.6	5.7	7.1	21.0
3	11.9	15.9	17.0	26.2
4	21.8	25.3	29.6	21.1
5	29.8	24.9	22.3	12.0
6	20.5	14.8	13.1	5.8
7	7.4	7.7	5.6	2.3
8	6.4	3.8	2.5	0.7
9	0.6	0.9	0.5	0.1
Rivaroxaban prescribed daily dose (mg)[c]				
10	3.8	6.2	3.5	5.1
15	51.6	43.5	27.1	21.1
20	44.6	50.3	69.4	73.8

Values are presented as mean ± standard deviation or %.

MB, major bleeding; CHA_2DS_2-VASc, congestive heart failure, hypertension, age > 75 years, diabetes mellitus, prior stroke or transient ischemic attack or systemic embolism, vascular disease, age 65 to 74 years, sex-female.

[a]Age is at time of MB. [b]Individual variables of interest identified within the 6-month period prior to MB for cases and within the 6-month period prior to end of study participation for non-MB patients. [c]The US Prescribing Information for patients with CrCl > 50 mL/min indicates that patients with nonvalvular AF take rivaroxaban 20 mg orally, once daily with the evening meal. For patients with CrCl 15 to 50 mL/min, the indicated dose is15 mg orally, once daily with the evening meal.[21]

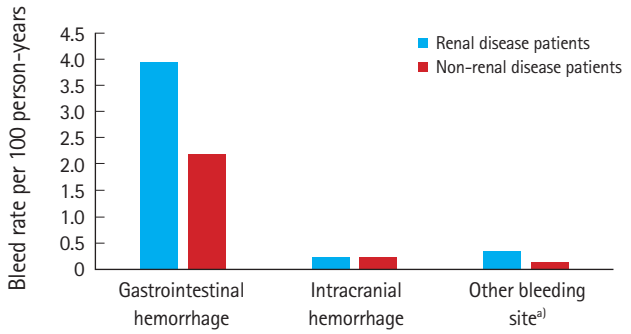

Fig. 1. Major bleeding rates by site and renal disease status. [a]'Other bleeding site' designation includes genitourinary bleeds and bleeds in unspecified sites.

among those without RD who experienced a MB, most were on a 20-mg dose (69.4%) followed by the 15-mg dose (27.1%).

The incidence rate of MB was higher among those with RD compared to those without RD, 4.52 per 100 person-years (95% CI, 4.05 to 5.05) versus 2.54 per 100 person-years (95% CI, 2.38 to 2.70), respectively. Comparing the MB rates by bleed site, rates were highest for bleeds of gastrointestinal origin regardless of RD status (Fig. 1). The incidence of intracranial bleeding was uncommon, with identical rates between RD and non-RD cohorts, 0.23 per 100 person-years (95% CI, 0.14 to 0.38) and 0.23 per 100 person-years (95% CI, 0.19 to 0.28), respectively.

Fatal outcomes were uncommon and occurred at an identical incidence in both the RD and non-RD cohorts, 0.09 per 100 person-years. The case fatality rate in those with RD was 1.9% (6/312) versus 3.6% (35/981) in those without RD. Patients with RD were older at time of death than those without RD, mean (standard deviation) age of 80.5 (6.3) versus 79.6 (8.1) years, respectively (Table 3). Regardless of RD status, patients with MB were managed similarly during their hospitalization in terms of length of stay, blood transfusion, intensive care unit care, and surgical interventions.

Table 3. MB event rates, bleed locations, hospitalization[a] and fatal outcomes data

Study finding	With renal disease (n = 312)	Without renal disease (n = 981)
MB incidence rate[b] per 100 person-years (95% CI)	4.52 (4.05–5.05)	2.54 (2.38–2.70)
MB with fatal outcome incidence rate (95% CI)	0.09 (0.04–0.19)	0.09 (0.07–0.13)
MB location		
Gastrointestinal hemorrhage	87.5	85.9
Intracranial hemorrhage	5.1	9.1
Genitourinary hemorrhage	0	1.1
Other	5.8	2.8
Unspecified	1.6	1.1
Length of hospitalization[c] (day)	4.2 ± 3.7	4.0 ± 3.5
Blood transfusion received	54.2	49.7
Transferred to intensive care unit	43.9	42.9
Surgical intervention needed	31.4	28.3
Fatal outcome[d]	6 (1.9)	35 (3.6)
Age at time of death (yr)	80.5 ± 6.3	79.6 ± 8.1

Values are presented as %, mean ± standard deviation, or number (%) unless otherwise indicated.
MB, major bleeding; CI, confidence interval.
[a]All MB cases were hospitalized due to the requirement within the case-finding algorithm used for the study. [b]The MB incidence rate was calculated using person-time for the denominator value (exposure time at risk) for all first MBs within the period under study. [c]Patients with MB who experienced fatal outcomes (n = 41) were excluded from length-of-stay analyses. [d]During hospitalization for the MB event.

DISCUSSION

In this observational study of 44,793 rivaroxaban users with nonvalvular AF, the incidence rate of MB for those with RD was higher than in those without RD, 4.52 vs. 2.54 per 100 person-years, respectively. The notably higher prevalence of comorbidities (e.g., hypertension, heart failure, coronary heart disease, and diabetes) in those with RD may, in part, explain the difference in MB rate between the two cohorts. Interestingly, MB and fatal outcome rates, as well as the patterns of bleeding (e.g., GI as the most common site) in relation to RD status were generally consistent with the findings for rivaroxaban-treated subjects from the clinical trial for rivaroxaban (Rivaroxaban Once daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation [ROCKET-AF]).[3]

Clinicians should be judicious when considering the effects of AF in patients with renal disorders, due to the increased risk for medical complications and death.[6,22] For example, in those with AF and chronic kidney disease (CKD), the incidence of stroke is distinctly higher across all stages of CKD.[6,23] Results from a recent meta-analysis of 28 studies showed that anticoagulation therapy was frequently withheld from patients with both AF and renal impairment, despite the need for stroke prevention.[9] However, there have been conflicting data published about the safety of anticoagulation therapy in those with AF and RD. A study by Abbott el al.[24] showed that the use of warfarin in chronic dialysis patients was correlated with reduced mortality in patients later hospitalized for AF. However, past studies have shown that patients with CKD, and particularly those with end-stage renal disease, have higher rates of bleeding complications when on anticoagulation therapy.[6,22,25] This was also noted in our analysis, as patients with RD sustained an increased risk of MB, though when we explored the diagnosis and procedure codes that were linked

with RD patients in our study, less than 2% were receiving dialysis, subsequently the number of patients with severe CKD/end-stage renal disease was likely extremely low.

For patients at high risk for both stroke and bleeding events, DOACs appear to have a net clinical benefit over warfarin.[21,26,27] In addition, DOACs are a promising alternative to warfarin, due to the fixed dosing, fewer drug-drug interactions, the absence of food interference, and little need for routine therapeutic monitoring.[1]

The DOACs all undergo metabolism by the kidneys to varying degrees.[28] Because these agents are partly eliminated by the kidneys, in patients with renal dysfunction there is both increased antithrombotic effects and increased risk of bleeding.[7] Challenges with DOACs include dosing modifications for patients with renal and impairments.[1,28] In this analysis, 43.9% of all RD patients received the 15-mg dose, which is the recommended dose for those with impaired renal function (defined as CrCl of 15 to 50 mL/min). It is unclear as to why over half of this RD cohort was prescribed 20 mg, or why a small proportion was prescribed the 10-mg dose, a dosage which is indicated for prophylaxis against venous thromboembolism in orthopedic surgery patients; this prescribing phenomenon may be due to unknown patient characteristics or clinician prescribing preferences.

In the ROCKET-AF clinical trial for rivaroxaban, the MB rate for the RD population ranged from 3.39 to 4.49 per 100 person-years, depending on level of renal dysfunction and dosing.[3] Findings from the present study reveal that the MB rate in those with RD is 4.52 per 100 person-years, among a real-world heterogeneous population of RD patients. The incidence of MB among those with RD in this post-market study is comparable to the findings from the registration trial for rivaroxaban.

General comparisons also can be made regarding MB incidence in RD populations from ROCKET-AF, this analysis, and clinical trial data from other DOACs. In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in atrial fibrillation trial of apixaban, renal impairment was correlated with increased risk of bleeding in patients with AF.[29] Incidence of MB increased as renal dysfunction increased; the MB rates ranged from 1.65% to 4.80% per year for those with renal function values ranging from >80 mL/min to ≤ 50 mL/min. All-cause mortality was three-fold higher in those with an estimated glomerular filtration rate (eGFR) of ≤ 50 mL/min compared to those with eGFR >80 mL/min, 7.71% vs. 2.52% per year.[29]

In the Randomized Evaluation of Long-term Anticoagulation Therapy trial of dabigatran, annual MB rates in those with renal dysfunction ranged from 1.98% to 5.48% per year.[30] The range of values was dependent on the level of renal dysfunction, with higher MB incidence associated with higher renal dysfunction (eGFR <50 mL/min). All-cause mortality also increased as renal dysfunction increased, ranging from 2.25%, 3.67% and 7.13% in the eGFR groups of ≥ 80, 50 to <80, and <50 mL/min, respectively.[30] Although caution is warranted when making cross-comparisons between clinical trials, it can be generally seen that the MB rate in the RD population in this study is comparable to the findings from the clinical trial data of rivaroxaban and other currently marketed DOAC agents.

Our study had several strengths. The MHS database used for this investigation represents a contemporary and large diverse cohort, which mirrors the population at large for many demographic and clinical characteristics, making the results of this study generalizable. The current analyses included the largest cohort of patients with nonvalvular atrial fibrillation exposed to rivaroxaban therapy to date in routine clinical practice. The data are robust and findings are generally consistent with the observations from large randomized trials.

The current study has limitations. This retrospective analysis was based on data points that were originally collected for EMR and accounting/claims purposes, rather than research. Additionally, pharmacy records capture the drug dispensing information rather than the actual administration of the drug, and connecting the use of rivaroxaban to a bleeding event only establishes temporal association rather than a causal relationship in any given individual. Importantly, the definition of RD was defined by administrative data, rather than an objective clinical measure of renal function. Our definition of RD was based solely on diagnosis codes, which was not based on a previously validated method. It is also unknown whether solely using diagnosis codes underestimated the cohort with minor disease and how this may have impacted our outcomes.

Additionally, MB events were only captured if they resulted in a hospitalization. While MB might be underreported due to limitations of the databases, there is also the possibility of capturing false positives, e.g., minor or clinically relevant bleeds that required medical attention.[15]

The definition for MB in this study is not an exact match with the clinical trial (ROCKET-AF)[26] definition as the algorithm is applied retrospectively and relies on the information available in the EMRs. The clinical trial definition of MB was defined as clinically overt bleeding with a fall in hemoglobin of 2 g/dL or more, or a transfusion of 2 or more units of packed red blood cells or whole blood, MB in a critical site, or a fatal outcome. That being noted, the rates and pattern of MB for those with RD are similar to the findings from the clinical trial for rivaroxaban, which implies that the MB case-finding methods are reasonable.

In this post-marketing study of 44,793 rivaroxaban users with

nonvalvular AF, those with RD experienced a higher rate of MB than those without RD. The fatal bleeding outcome rate was identical between the MB cohorts with and without RD. Clinical management of MB cases was also similar between the two cohorts. The higher rate of MB found in this study among those with RD may be due to the confounding effects of comorbidities, as those with RD had a higher prevalence of comorbidities compared to those without RD. The incidence of MB in this diverse population of rivaroxaban users with RD was similar to the findings from the clinical trial of rivaroxaban.

CONFLICT OF INTEREST

This study is funded by Janssen Scientific Affairs, LLC and Bayer HealthCare. Dr. Yuan is a salaried employee of Janssen Research & Development, LLC, and owns stocks of Johnson & Johnson. Dr. Patel reports grants from Janssen and Johnson and Johnson, and personal fees from Bayer. Outside of the submitted work, Dr. Patel reports grants from Heart Flow Technologies, Astra Zeneca, NHLBI, and AHRQ, and personal fees from Astra Zeneca and Otsuka. Dr. Peacock reports Consultant and Research Grant from Janssen, Consultant for Bayer. Outside of the submitted work, Dr. Peacock reports research grants from Abbott, Alere, Banyan, Cardiorentis, Portola, Pfizer, Roche, the Medicine's Company, ZS Pharma. Consultant with Alere, Cardiorentis, Ischemia Care, Phillips, Portola, Prevencio, The Medicine's Company, ZS Pharma. Ownership interests in Comprehensive Research Associates LLC, Emergencies in Medicine LLC. CAPT Tamayo has no conflicts of interest to disclose. Mr. Sicignano is an employee of Health ResearchTx LLC, which has a business relationship with Janssen Research and Development. Ms. Hopf reports receipt of professional fees (for medical writing services) from Health ResearchTx LLC during the conduct of the study. Health ResearchTx has a business relationship with Janssen.

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