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Rivaroxaban prescribing in a Saudi tertiary care teaching hospital

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ABSTRACT

Purpose: This drug utilization review (DUR) aimed to describe the use of rivaroxaban in a tertiary care teaching hospital and to audit the hospital physicians' prescribing practice.
Methods: This study reviewed rivaroxaban prescriptions for patients admitted to a tertiary care teaching hospital in Riyadh, Saudi Arabia, between October 1, 2016 and January 15, 2017. It included all in-patients who received at least one dose of rivaroxaban, using data from the hospital's health information system (HIS). Appropriateness of prescribing was evaluated based on documented indication, dosing according to the patient's renal function for each approved indication, and restriction policy as per hospital department.
Results: During the study period, a total of 343 rivaroxaban prescriptions for 322 patients were identified. Overall, more than 56% of rivaroxaban prescriptions met at least one inappropriate criterion. Inappropriate dosing per patient's creatinine clearance (CrCl) was recognized in 42% of rivaroxaban prescriptions with the majority of these prescriptions issued for lower doses in 82.9% of prescriptions and non-approved indications identified in 14% of rivaroxaban prescriptions.
Conclusions: The introduction of oral rivaroxaban represents a paradigm shift in anticoagulation management. Future longer, larger multi-center research is needed to identify the most effective interventions to enhance rivaroxaban knowledge translation and reduce the likelihood of inappropriate rivaroxaban prescribing and associated economic and side effects sequelae.

1. Introduction

Anticoagulant medications are primarily used to prevent and treat systemic embolism associated with atrial fibrillation (Afib) and venous thromboembolism (VTE), which includes stroke, deep-vein thrombosis (DVT), and pulmonary embolism (PE). They are also used to prevent post-surgical thromboembolism in patients following hip, knee, and mitral valve replacement surgery (Greinacher, Thiele, & Selleng, 2015; Harder & Graff, 2013) and with Protein C and S or Factor V Leiden deficiencies (Kujovich, 2011). Until early 2010, warfarin was the only available oral anticoagulant (Ageno et al., 2012; Schulman, 2014). However, warfarin has a very narrow therapeutic window that requires routine coagulation monitoring through international normalized ratio (INR) and dose adjustment to avoid increased risk of thrombosis and bleeding, its slow-onset action requires bridging therapy with heparin, its unpredictable pharmacodynamics and pharmacokinetics need constant laboratory monitoring, which is inconvenient and costly, and it interacts with several different food types that necessitate lifestyle changes (Johnson et al., 2011). In light of these limitations, alternative oral anticoagulants were developed that are at least as effective as warfarin, but have more predictable pharmacokinetics, are easier to administer at fixed doses with rapid-onset action, and have fewer food-drug or drug-drug interactions.

Rivaroxaban was developed by directly blocking the Xa effect on a single factor within the coagulation cascade. It absorbs rapidly with maximum plasma concentration achieved within 2–4 h.

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A 10 mg (mg) dose has 80–100% oral bioavailability with or without food and about 60% bioavailability for 15 mg and 20 mg doses if a patient is fasting. Higher doses should be taken with food to assure complete absorption (Kreutz, 2014; Mueck, Stampfuss, Kubitza, & Becka, 2014). The drug has a half-life of 5–9 h in healthy individuals aged 20 to 45 and 11–13 h in elderly persons. It has a dual mode of elimination, with two-thirds undergoing metabolic degradation via CYP3A4, CYP3A5, and CYP2J2, and the remaining third excreted via the kidneys as unchanged drug. Thus, dose adjustment is required in patients with creatinine clearance (CrCl) of less than 50 ml/min (Carter & Plosker, 2013; Spencer & Amerena, 2015). Co-administration of rivaroxaban should be avoided with potent P-glycoprotein inhibitors/inducer and CYP3A4 inhibitors/inducer to prevent increased risk of bleeding or thromboembolism (Burness & Perry, 2014; Mueck, Kubitza, & Becka, 2013; Thomas, Ganetsky, & Spinler, 2013).

Rivaroxaban is generally well-tolerated; however, bleeding is the most frequently reported side effects. Other reported side effects include headache, tinnitus, pyrexia, fatigue, dizziness, shoulder pain, vomiting, nausea, constipation, and abnormal liver function test (Abrams & Emerson, 2009; Duggan, Scott, & Plosker, 2009). Rivaroxaban is contraindicated in pregnant and breastfeeding women and in patients with clinically significant bleeding (e.g. gastrointestinal or intracerebral) within the past six months, active peptic ulcer, neurosurgery within the past four weeks, or a known bleeding disorder. Bleeding risk increases in patients with thrombocytopenia, receiving concomitant non-steroidal anti-inflammatory drugs (NSAIDs), renal impairment with CrCL < 15 ml/min, and some malignancies (Burness & Perry, 2014; European Medicines Agency (EMA), 2008; Harder & Graff, 2013; Verma & Brighton, 2009).

Rivaroxaban is approved worldwide for the treatment of various thromboembolic conditions. The European Medicines Agency (EMA) approved it for VTE prophylaxis in adult patients undergoing hip or knee replacement surgery in 2008 (European Medicines Agency (EMA), 2008). In 2009, Health Canada (HC) approved it for VTE prevention in patients after orthopedic surgery, and the US Food and Drug Administration (FDA) advisory panel approved it for VTE prophylaxis in patients after orthopedic surgery, after requesting additional manufacturing data. In 2012, the EMA and the FDA approved rivaroxaban to prevent stroke and embolism in adult patients with non-valvular AFib (NVAF) and to treat DVT and PE (European Medicines Agency (EMA), 2012; Food and Drug Administration (FDA), 2012).

Rivaroxaban is available in the Saudi market in three different strengths—10, 15, and 20 mg tablets—although there are no published data on how hospital physicians are using it. The various guidelines and recommendations support warfarin use as first-line therapy in different coagulopathy states, but also encourage rivaroxaban use as an alternative treatment for VTE prophylaxis, as well as for stroke and embolism prevention (Camm et al., 2012; January et al., 2014; Kearon et al., 2016). Therefore, it is crucial to assess its use within the clinical setting to ensure prescribing appropriateness, safety, efficacy, and to identify areas for improvement.

For newly approved drugs such as rivaroxaban, DURs are strongly recommended to evaluate physicians' prescribing behavior, to identify physicians that are more likely to prescribe suboptimally, to provide measures information for healthcare system planning and procurement, and as an indicator for quality management for accreditation purposes as per the Anticoagulation Forum consensus statement recommendations (Jobski et al., 2014; Schneeweiss & Avorn, 2005; The Joint Commission, 2017). This DUR aimed to describe how rivaroxaban was prescribed in a tertiary care teaching hospital and to audit the hospital physicians' prescribing practice.

2. Methods

2.1. Study design and setting

The study was a mono-centric, descriptive, retrospective, cross-sectional DUR for rivaroxaban, conducted at King Saud University Medical City (KSUMC), a 1000-bed tertiary care teaching hospital in Riyadh, Saudi Arabia. It looked at rivaroxaban as a formulary medication with prescribing restrictions for hematology and cardiology departments who are also responsible for authorizing its prescribing by other departments such as orthopedic surgery and internal medicine. The study utilized data from patients' electronic medical records (EMRs) and from the hospital's health information system (HIS) to evaluate the prescriptions of all patients admitted at KSUMC and prescribed rivaroxaban from October 1, 2016 to January 15, 2017. Patients were excluded from the study if they were prescribed rivaroxaban beyond the study period. Institutional Review Board (IRB) approval was obtained from KSUMC with project number (E-17-2747).

2.2. Patients' data

Data extracted from the HIS included patient age, gender, rivaroxaban indication, dose, frequency, treatment duration, refill orders, total dispensed quantity, duration of rivaroxaban per quantity expressed in days, prescriber medical department, and patient weight, height, and serum creatinine (Scr).

2.3. Prescribing appropriateness

Rivaroxaban appropriateness was evaluated, with prescribing labeled inappropriate if one or more of the following criteria were met: non-adherence to the recommended dose for each approved indication as per renal function and manufacturer recommended dosing for prophylactic or therapeutic indications; any dose not prescribed based on CrCl calculation or documented Scr; non-adherence to the recommended and approved indications; prescription without indication; and non-adherence to restriction policy as per medical department. Approved indications included to reduce the risk of stroke and systemic embolism in NVAF, treatment of DVT and PE, and prevention of prophylaxis after hip and knee surgery.

In line with clinical studies used to approve rivaroxaban (Bauersachs et al., 2010; Büller et al., 2012; Patel et al., 2011), the Cockcroft–Gault equation was used to calculate the patient's CrCl at rivaroxaban initiation, using the patient's Scr and actual body weight to evaluate dosing per renal function. Adjusted body weight was used to calculate the CrCl in obese patients.

2.4. Statistical analysis

Descriptive statistics, including means, standard deviations (SDs), frequencies and percentages were calculated. Categorical variables were expressed as frequencies and percentages while continuous variables were expressed as means and SDs. Results were presented in tables. All statistical analyses were performed with IBM SPSS Statistics for Windows, version 24.0 (Armonk, NY: IBM Corp, 2016).

3. Results

A total of 343 rivaroxaban prescriptions for 322 patients were evaluated over the data collection period. Baseline characteristics for rivaroxaban users are depicted in Table 1. The mean age was 58.96 ± 17.25 with a larger proportion of prescriptions identified

Table 1
Baseline characteristics of rivaroxaban users.

Patients characteristics	Female N (%)	Male N (%)	Total N (%)
Gender	196 (61)	126 (39)	322 (1 0 0)
Age (mean ± SD) Years	56.71 ± 17.77	60.64 ± 16.81	(58.96 ± 17.25)
Age group			
18–39 years	34 (17.3)	16 (12.7)	50 (15.5)
40–59 years	59 (30.1)	37 (29.4)	96 (29.8)
60–79 years	83 (42.3)	58 (46)	141 (43.8)
≥80 years	20 (10.2)	15 (11.9)	35 (10.9)
Total	**196 (1 0 0)**	**126 (1 0 0)**	**322 (1 0 0)**
Weight group			
≤40 kg	3 (1.5)	1 (0.8)	4 (1.2)
41–60 kg	14 (7.1)	15 (11.9)	29 (9)
61–80 kg	82 (42)	47 (37.3)	129 (40.1)
81–100 kg	57 (29.1)	31 (24.6)	88 (27.3)
>100 kg	21 (10.7)	19 (15.1)	40 (12.4)
Not recorded	19 (9.7)	13 (10.3)	32 (10)
Total	**196 (1 0 0)**	**126 (1 0 0)**	**322 (1 0 0)**
CrCl level			
<50	12 (5.5)	14 (11.1)	26 (7.6)
≥50	172 (79.3)	83 (65.9)	255 (79.2)
Missing	33 (15.2)	29 (23)	62 (19.3)
Total	**217 (1 0 0)**	**126 (1 0 0)**	**343 (1 0 0)**

Table 3
Audit of rivaroxaban prescriptions based on appropriateness criteria.

Appropriateness criteria	N (%)
Overall appropriateness (N = 343)	
Appropriate	149 (43.4)
Inappropriate	194 (56.6)
Appropriateness according to dose per CrCL (N = 343)	
Appropriate dose	199 (58)
Inappropriate dose (with/without CrCl)	143 (41.7)
Inappropriate lower dose (with CrCl)	68/82 (82.9)
Inappropriate higher dose (with CrCl)	12/82 (14.6)
Doses without indication (with CrCl)	2/82 (2.4)
Appropriateness according to approved indication (N = 343)	
Appropriate indication	258 (75.2)
Inappropriate indication	85 (24.8)
Appropriateness according to overall appropriateness and medical specialty (N = 149)	
Cardiologists	64 (43)
Hematologists	54 (36.2)
Inappropriateness according to medical department (N = 194)	
Department not recorded	37 (19.1)
Cardiology	80 (41.2)
Hematology	51 (26.3)
Orthopedic surgery	13 (6.7)
Internal Medicine	13 (6.7)

in female patients (196, 61%), in patients aged 60–79 (141, 43.8%), and in patients weighing 61–80 kg (129, 40.1%). Three-quarters of patients (255, 79.2%) had a CrCl greater than 50 ml/min, whereas the Scr level was never requested for approximately one-fifth of patients (62, 19.3%) throughout rivaroxaban therapy.

Rivaroxaban prescription characteristics are shown in Table 2. The 20 mg dose was the most commonly prescribed strength (197, 57.4%). Almost all the patients (328, 95.6%) received rivaroxaban once daily. In terms of appropriate use per indications, 139 (40.5%) received rivaroxaban for NAVF, 76 (22.2%) for DVT, and 35 (10.2%) for PE. Approximately one-tenth of the patients (37, 10.8%) received rivaroxaban without any apparent indications, 210 (61.2%) received rivaroxaban for an indefinite duration, while 107 patients (31.2%) received either a prescription without information about duration or frequency less than 35 days, which is the shortest treatment length per manufacturer recommendations. The majority of the prescribers were cardiologists (144, 42%) and hematologists (105, 30.6%).

Appropriateness of rivaroxaban prescribing is reported in Table 3. It was appropriately used based on overall approved indications for (149, 43.4%) patients. If rivaroxaban was given based only on manufacturer recommended renal function dosing, i.e. CrCL, (199, 58%) received it appropriately. If rivaroxaban was given based only on indication, (258, 75.2%) received it appropriately. Based on overall approved indications, (64, 43%) cardiologists and (54, 36.2%) hematologists prescribed rivaroxaban appropriately.

Table 2
Rivaroxaban prescriptions characteristics.

Prescriptions characteristics	N (%)
Strength	
10 mg	64 (18.6)
15 mg	82 (24)
20 mg	197 (57.4)
Frequency of prescribing	
Once daily	328 (95.6)
Twice daily	15 (4.4)
Indications	
Undocumented indication	37 (10.8)
DVT	76 (22.2)
PE	35 (10.2)
NVAF	139 (40.5)
Knee replacement prophylaxis	8 (2.3)
Non-approved indications	48 (14)
Treatment duration	
No information	88 (25.7)
35 days	5 (1.5)
3 weeks or less	19 (5.5)
3 months	11 (3.2)
6 months	10 (2.9)
Indefinite	210 (61.2)
Prescribing department	
No recorded	52 (15.1)
Cardiology	144 (42)
Oncology	1 (0.3)
Hematology	105 (30.6)
Orthopedic	16 (4.7)
Pulmonology	4 (1.2)
Internal Medicine	21 (6.1)

4. Discussion

This retrospective DUR identified a high proportion of inappropriate prescribing of rivaroxaban in a tertiary care teaching hospital. More than half of the rivaroxaban prescriptions met at least one inappropriate criterion. The most common issues noted in physicians' prescribing were inappropriate dosing and inappropriate indications.

In the DUR, inappropriate dosing of rivaroxaban per CrCl accounted for 144/343 prescriptions (42%). Remarkably, a high percentage of rivaroxaban inappropriate dosing [82.9% (68/82)] was written for a reduced dose from that recommended by the manufacturer among patients with documented Scr with different indications except in knee replacement prophylaxis where more than half of these patients were prescribed a higher dose than recommended by the manufacturer (European Medicines Agency (EMA), 2012; Food and Drug Administration (FDA), 2012).

Our result concurs with the result from Whitworth et al. who demonstrated that 34.8% of patients on rivaroxaban received inappropriate dosing, with the majority of these doses lower than current prescribing recommendations (Whitworth et al., 2017). Another study by Simon et al. evaluated recognized the prescribing of low dose rivaroxaban as an inappropriate practice in only 2.8% of

the study population; however, this number is a long way from our finding (Simon, Hawes, Deyo, & Bryant Shilliday, 2015). Our result is also in line with the findings from Tellor et al.'s study who reported inappropriate rivaroxaban dosing in 92 (35.4%) NVAF patients of whom 41 received too low a dose and 51 received too high a dose, taking into account the patient's renal function at the initiation of rivaroxaban (Tellor, Patel, Armbruster, & Daly, 2015). However, our result contrasts with two studies. First, a study carried out by Isaacs et al. who reported 92% appropriateness in rivaroxaban dosing in patients with normal renal function and 79% appropriateness in patients with renal dysfunction (Isaacs, Doolin, Morse, Shiltz, & Nisly, 2016). Second, Chowdhry et al. conducted a study and the results showed that only 2% of rivaroxaban was associated with inappropriate high dose (Chowdhry, Jacques, Karovitch, Giguere, & Nguyen, 2016). In our study, dosing accuracy could not be established in some patients due to lack of baseline renal function assessment by physicians, which resulted in another form of inappropriate prescribing practice. This is consistent with the result from Simon et al. who concluded that over one-third of study patients received rivaroxaban without an assessment of baseline Scr at the time of prescribing (Simon et al., 2015). One possible explanation concerning frequent inappropriate dosing of rivaroxaban is that dosing must be based on the patient's CrCl, which requires information on patient weight, age, and laboratory results for Scr, which sometimes are not recorded or requested on patient admission or cannot be measured in some bedridden patients. Therefore, caution must be exercised when prescribing rivaroxaban, particularly in patients with renal dysfunction, to avoid thrombosis from lower dose or bleeding from excessive dose. Another possible explanation might be related to physicians' fear of bleeding risk, particularly as rivaroxaban is a relatively new drug and usually it takes physicians years until they become familiar with a new drug's safety and efficacy profile.

Another notable concern in rivaroxaban prescribing was related to indication inappropriateness, which was identified in almost one-quarter of patients' prescriptions. This type of inappropriateness consisted of two forms: non-approved indications, which accounted for the most indication inappropriateness in this study (14%), and undocumented indication (10.8%). In this study, 48 rivaroxaban prescriptions were issued for non-approved indications with the majority prescribed for cerebral vein thrombosis in 12 patients (25%) and portal vein thrombosis in 11 patients (22.9%). Non-approved rivaroxaban indications were categorized as follows: thrombotic events other than lower extremities deep veins and pulmonary arteries; cerebrovascular disease; surgical prophylaxis other than hip and knee prophylaxis, or history of arrhythmias. This finding is supported by Tellor et al., who identified 16 patients treated for off-label indications and not evaluated for appropriateness in their study (Tellor et al., 2015), and by Isaacs et al., who found 11 patients (17.7%) who were discharged on rivaroxaban (Isaacs et al., 2016). Further, Chowdhry et al. reported that 45 patients (78%) received rivaroxaban for non-approved indications (Chowdhry et al., 2016) and a study conducted in Germany by Jobski et al. who reported the use of rivaroxaban for non-approved orthopedic surgery and cardiovascular indications in 8.9% (39 patients) and 2.5% (11 patients) respectively and unknown indication in 6.1% (27 patients) (Jobski et al., 2014). Clinical indication plays a major role in rivaroxaban prescribing as it can determine appropriate dose and duration of therapy as well as limit the risk of bleeding or clotting. Although prescribing rivaroxaban for non-approved indications seems a reasonable decision in certain clinical situations where there is no alternative, it may predispose patients to a high risk of major bleeding when benefit is indefinite (Smythe et al., 2013). Moreover, this practice may disseminate biased and confusing information for physicians, not to mention that it can be a form of malpractice. Use of rivaroxaban should therefore be limited to approved indications by regulatory bodies which require availability of clinical trial results about rivaroxaban safety and efficacy in these non-approved indications, or it should be referred to the Pharmacy and Therapeutics Committee (PTC) to grant approval per patient case. Until that time, non-approved use should be discouraged and discussed with physicians (Smythe et al., 2013). In this study, a possible explanation for prescribing rivaroxaban for non-approved indications is confusion with the traditional therapy, warfarin, which is used for a wide range of coagulopathy disorders. Another possible explanation is that patients might have either drug-drug or drug-disease interactions or contraindications which prevent them from using traditional anticoagulants, so rivaroxaban is prescribed as a safe alternative drug.

With regard to sites of care and rivaroxaban prescribing, cardiology followed by hematology were the two medical departments with the highest rates of rivaroxaban prescribing as well as the departments with the greatest risk of inappropriate rivaroxaban prescribing. Several prescriptions were written from unauthorized services such as oncology (0.3%) or pulmonary (1.2%), which is considered another form of inappropriateness since rivaroxaban is restricted to specialized services such as cardiologist and orthopedic surgeons. This finding was consistent with that of Chowdhry et al., who showed that orthopedic surgery was the most frequently prescribing department for rivaroxaban followed by medicine departments including cardiology. This was because rivaroxaban was most commonly used in Chowdhry et al.'s study to prevent VTE in patients undergoing elective hip or knee surgery compared with other new oral anticoagulants, which were used mainly for prevention of stroke and systemic embolism in patients with Afib (Chowdhry et al., 2016). Additionally, many unrecorded medical departments had a high rate of prescribing and inappropriateness. This mandates establishing structured educational programs targeted to these departments to promote the appropriate use of rivaroxaban in addition to referring complicated cases in which rivaroxaban is indicated to specialty services or clinical pharmacists.

To improve practice, the hospital should develop and disseminate evidence-based protocols to enlighten physicians about appropriate rivaroxaban prescribing with regards to indications and dosing per CrCl, to set the policy and procedure to be enforced, to ensure that services are authorized to prescribe rivaroxaban, and to provide a targeted education program for unauthorized services with an option to consult specialty services in order to increase patient safety. Other initiatives might include pharmacist-directed interventions mainly in providing consultations about the appropriate use of rivaroxaban in general and in renal failure patients in particular as well as hospital prescribing protocol particularly for non-specialized medical services; alert information appearing as a pop-up screen during order entry to remind physicians about rivaroxaban prescribing protocol and dosing per indication and according to patients' calculated CrCl; and the introduction of a drug utilization program to evaluate and audit physicians' prescribing to identify and address many of the challenges associated with high-risk drugs use.

This DUR is the first to evaluate the use of rivaroxaban within a tertiary care teaching hospital in Saudi Arabia, using the EMR database to capture all patients who received a prescription of rivaroxaban within the study period and to avoid selection bias; however, it is not without limitations. First, this was a mono-centric study with a relatively small number of prescriptions and shorter duration. Second, due to the retrospective EMR nature of this study, our results may be confounded by incomplete documentation and capture of patient and/or prescription information by physicians.

5. Conclusions

Overall, this study provides a first insight at prescribing patterns in Riyadh, Saudi Arabia, and demonstrates an increase in the proportion of inappropriate rivaroxaban prescribing, mainly as a result of unapproved indication and inappropriate dosing based on renal function, which can potentially harm patients. These results highlight the importance of physicians' education regarding appropriateness, indication, and dosing of rivaroxaban as well as the value of a continuous drug utilization program to monitor high-risk medications especially at the early stages of drug approval and adoption by physicians. Further research is warranted to fully elucidate the consequences of inappropriate rivaroxaban prescribing as well as the impact of interventions on improving rivaroxaban prescribing using implementation research.

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There are no relevant disclosures or conflicts of interest.

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