مستشفى الملك فيصل التخصصي ومركز الأبحاث
King Faisal Specialist Hospital & Research Centre
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Pharmacy Newsletter

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Surviving the Evidence Appraisal Controversy: Rivaroxaban in Acute Coronary Syndrome as a Case Study

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On discussing appraisal controversies, it is essential to adapt a reliable approach to determine the value of debates on reviewing scientific and clinical evidence. An appraisal must be performed impartiality with objectivity and independence, free from bias of personal interests. The contribution of a reputable expert appraiser can provide an evaluation with greater credibility. On the other hand, poorly prepared or insufficiently guided experts can weaken an appraisal and negatively impact the property owner for years.

Cardiovascular mortality has been greatly reduced over the past 50 years, yet cardiovascular disease is expected to remain a leading cause of death worldwide over the next two decades. Most patients who present with an acute coronary syndrome (ACS) are expected to survive the initial event and live a good quality life. However, a small but substantial proportion of patients will present with recurrent ischemic events despite standard medical therapy, including long-term antiplatelet therapy with aspirin and an adenosine diphosphate–receptor inhibitor. This risk may be related in part to excess thrombin generation that persists beyond the acute presentation in such patients. As a result, there has been a growing interest in evaluating the role of oral anticoagulants after an ACS. Improved cardiovascular outcomes were reported for patients who were treated with the anticoagulant warfarin in addition to aspirin. However, widespread use of long-term warfarin in such patients has been limited by challenges associated with drug monitoring and the risk of bleeding. Likewise, treatment with factor IIa inhibitor ximelagatran after a myocardial infarction showed cardiovascular benefits, but the drug was associated with hepatotoxicity.

Rivaroxaban is a novel oral anticoagulant that directly antagonizes factor Xa and is a reversible inhibitor of the factor Xa active site. By inhibiting factor Xa, rivaroxaban is able to block the final processes of the coagulation cascade.

Rivaroxaban is approved by the US Food and Drug Administration (FDA) for the management of deep vein thrombosis (DVT) prophylaxis that may lead to pulmonary embolism (PE) in patients undergoing hip or knee replacement surgery. Subsequently, rivaroxaban was approved for reducing the risk of stroke in non-valvular atrial fibrillation in 2011.

ATLAS ACS–TIMI 46 was the first study to evaluate the addition of anti-factor Xa rivaroxaban to standard therapy in participants with ACS. It is a phase II dose-finding trial, that enrolled 3,491 patients with a recent ACS diagnosis. Rivaroxaban was tested at total daily doses ranging from 5 to 20 mg, compared with placebo. The primary efficacy endpoint was death, myocardial infarction, stroke, or severe recurrent ischemia requiring revascularization during 6 months. The primary safety endpoint was clinically significant bleeding, such as thrombosis in myocardial infarction (TIMI major, TIMI minor or requiring medical attention). Rates of the primary efficacy endpoint were 5.6% rivaroxaban versus 7.0% placebo (Hazard Ratio [HR] 0.79, p=0.10). The risk of clinically significant bleeding with rivaroxaban versus placebo increased in a dose-dependent manner HR 2.21 [95% CI 1.25–3.91] for 5 mg, 3.35 [95% CI 2.31–4.87] for 10 mg, 3.60 [95% CI 2.32–5.58] for 15 mg and 5.06 [95% CI 3.45–7.42] for 20 mg doses; p<0.0001. Rivaroxaban reduced the main secondary efficacy endpoint of death, myocardial infarction, or stroke compared with placebo by RRR=29%, ARR= 1.6%, NNT= 62, p=0.0270.

On the basis of these observations the ATLAS ACS 2–TIMI 51 study was conducted. It is a phase III study analyzing the effect of low-dose rivaroxaban as adjunctive therapy in the same patient population. The trial tested the hypothesis that inhibition of factor Xa with low-dose rivaroxaban 2.5 mg or 5 mg twice daily, might improve cardiovascular outcomes in patients with a recent ACS. A total of 15,526 patients were enrolled with a recent ACS to receive twice-daily doses of either 2.5 mg or 5 mg of rivaroxaban or placebo, for a mean of 13 months, and up to 31 months.

Continued on Page 6

In this issue

(references available on request)

Formulary & Therapeutics Committee Updates

The following are formulary changes by the Formulary & Therapeutics Committee (FTC) from Jan-Mar 2017 meetings. Please refer to the Online Hospital Formulary to check the status of the new medications and details on dosing and uses.

Approved New Formulary Additions

- **Antihemophilic Factor (Recombinant) Fc fusion (Eloctate®) 250, 500, 1000 unit vials**

  Treatment and prophylaxis of bleeding in patients with hemophilia A (congenital factor VIII deficiency). Prescribing restricted to adult and pediatric hematology/oncology consultants.

- **Ferric Carboxymaltose 500 mg injection**

  Treatment of iron deficiency and iron deficiency anemia in adult non-hemodialysis patients who need IV iron replacement.

Approved Expansion of Indication and Waiver of Form B

- **Cabergoline (Dosintex®)**

  Treatment of Cushing's syndrome.

Approved Changes of Prescribing Restrictions

- **Quetiapine (Seroquel®)**

  Treatment of ICU delirium . Prescribing restricted to ICU physicians and neurologists.

New/Updated Guidelines

- **Drug induced QTc Prolongation Monitoring Guidelines for Patients at KFSH&RC**

  New guideline in alignment with the AHA/ACC for initiation, prescribing and monitoring medications that may lead to Tosades de pointes (Tdp). The guideline describes the monitoring recommendations for medications that prolong the QTc interval.

- **Guidelines for Hepatitis C Virus (HCV) Treatment with Directly Acting Antivirals (DAAs)**

  Updated to include indication for treatment in patients with previous failure of DAAs.

- **Treatment Guidelines for Adult Patients with Pulmonary Arterial Hypertension (Bosentan, Macitentan, Iloprost and Sildenafil)**

  Updated to standardize the treatment guidelines for adult patients with pulmonary arterial hypertension.

- **Prescribing Guidelines for Oral Mycophenolate Mofetil (Cellcept®) for Adult and Childhood Lupus Nephritis Treatment**

  New guideline to expand indications and age group (children) to standardize patient care and highlight monitoring parameters.

- **Guidelines for use of Mycophenolate Mofetil (Cellcept®) Prophylaxis and Treatment of Acute GVHD in Pediatrics Allogenic Stem Cell Transplantation**

  New medication guideline for this indication including pediatric age group.

- **Vaccine Administration Guidelines**

  Updated guideline to include recommendations for Hepatitis A (Vaqta®) as a temporary alternative for Avaxim® and Hexaxim® as a temporary alternative to Pediacel®.

Approved and Updated Central Policy and Procedures (CPP)

- Restricted Formulary Medications (MCO-CS-PCS-07-004).
- Unlicensed/ Unapproved Use of Medications (MCO-CS-PCS-07-009).
- Process of Formulary Request Evaluation (MCO-CS-PCS-07-017).
- Special Forms for Selected Formulary Medications (MCO-CS-PCs-07-006).
- Temporary Formulary Medications (MCO-CS-PCS-07-030).
- IVIG Prescribing Process (MCO-CS-PCS-07-007).
- Workflow of Formulary and Therapeutics Committee and its Subcommittees (MCO-CS-PCS-07-001).
- Process of Adding and Deleting a Medication/Dosage Form to/from the Formulary (MCO-CS-PCS-07-002).
- Drug Samples (MCO-CS-PCS-07-011).
- Medication Use Evaluation Program (MCO-Cs-PCS-07-019).
- Prescribing Antineoplastic Drugs (MCO-CS-PCS-07-074).

Retired Central Policy and Procedures (CPP)

- Deleting a Medication from the Formulary– amalgamated with CPP# MCO-CS-PCS-07-002.
- Antimicrobial Utilization and Evaluation (AUE) Subcommittee– amalgamated with CPP# MCO-CS-PCS-07-001.

Approved ProVation Care-Sets

- Asthma, Initial Assessment.
- Inguinal or Femoral Hernia Repair, Postoperative.
- Minor General Surgery, Postoperative.
- Appendectomy, Postoperative.
- Cholecystectomy, Postoperative.

For more information on the indications, age specifications, doses and guidelines please check the online hospital formulary: http://online.lexi.com/lco/action/home

TRAINING AND MENTORSHIP IN PHARMACY PROFESSION

BUILDING AN INTEGRATED MODEL

مستشفى الملك فيصل التخصصي و مركز الأبحاث
King Faisal Specialist Hospital & Research Centre
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NOVEMBER 1 & 2
2017

KING FAISAL SPECIALIST HOSPITAL AND RESEARCH CENTER RIYADH, SAUDI ARABIA

OBJECTIVES

- Build an integrated and practical model for pharmacy training and mentorship
- Define standards for undergraduate and postgraduate training programs in Saudi Arabia
- Discuss best practice models in pharmacy education and training
- Review local and international practice models in pharmacy training
- Recommend steps on how to build new training programs or refine the existing ones
- Discuss preceptors development programs and staff engagement initiatives

TOPICS

- The impact of structured pharmacy training on overall health care in the kingdom
- Mentorship and pharmacy training
- The key components for successful training programs
- Advancing pharmacy related research
- International and local residency programs
- International and local perspectives on accreditation

WORKSHOPS

- Mentorship
- Pharmacy Residency Programs Local and International Accreditation

TARGET AUDIENCE

- Pharmacists
- Pharmacy trainees and residents
- Academia
- Government personnel
- Pharmacy students
- Pharmacy technicians
- Other healthcare providers

KING FAISAL SPECIALIST HOSPITAL AND RESEARCH CENTER (KFSHRC) IS ACCREDITED BY THE ACCREDITATION COUNCIL FOR PHARMACY EDUCATION AS A PROVIDER OF CONTINUING PHARMACY EDUCATION

What is in the News

Gadolinium Accumulation in the Brain Following Multiple Contrast Enhanced MRI

Health Canada has conducted a safety review of gadolinium-based contrast agents (GBCAs) due to growing scientific evidence that it may accumulate in the brain following multiple contrast-enhanced magnetic resonance imaging (MRI) scans. It is eliminated renally, but small amounts may remain in different body organs, including the brain. Accumulation in the brain has been found in patients with or without kidney disease. Health care providers are advised to use the lowest effective dose of GBCAs and limit its use only when a contrast agent is considered necessary.

Risk of Hepatitis B Viral Reactivation with the use of Lenalidomide (Revlimid®)

SFDA is warning about the viral reactivation that has been reported in some cases following treatment with lenalidomide, particularly in patients who have been previously infected with herpes zoster or HBV. Some cases resulted in acute hepatic failure or a fatal outcome. These cases have been reported very rarely (<1/10,000), but in four cases they progressed to hepatic failure. Reactivation of herpes zoster in some cases led to disseminated herpes zoster, meningitis herpes zoster or ophthalmic herpes zoster. These cases required antiviral treatment and the permanent discontinuation or temporary interruption of treatment with lenalidomide.

Rare and Serious Allergic Reactions with Antiseptic Products Containing Chlorhexidine Gluconate

FDA is warning that rare but serious allergic reactions have been reported with products containing chlorhexidine gluconate. The number of reports of serious allergic reactions has increased over the last several years with these products. These products are available as solutions, washes, sponges, swabs, prescription mouthwash to treat gingivitis, and as a prescription oral chip to treat periodontal disease. Healthcare providers are advised to ask patients of any previous allergic reactions to any antiseptic before recommending or prescribing a chlorhexidine gluconate product, and to consider using alternative antiseptics when any previous allergy to chlorhexidine gluconate has been documented or is suspected.

Rare Cases of Disabling and Persistent Serious Adverse Reactions with Fluoroquinolones

Cases of disabling and persistent serious adverse reactions mostly involving the musculoskeletal system, peripheral neuropathy, and central nervous system disorders have been reported when using oral or parenteral fluoroquinolones.

The reported adverse reactions include: tendonitis, achilles tendon rupture, peripheral neuropathy, depression, anxiety, dizziness and confusion. Healthcare providers are advised to stop systemic fluoroquinolone treatment if a patient reports a serious adverse reaction and should be aware that adverse reactions can occur within hours to weeks after exposure to treatment. Patient's treatment should be switched to an alternative treatment with a non-fluoroquinolone antibacterial drug if needed to complete the treatment course.

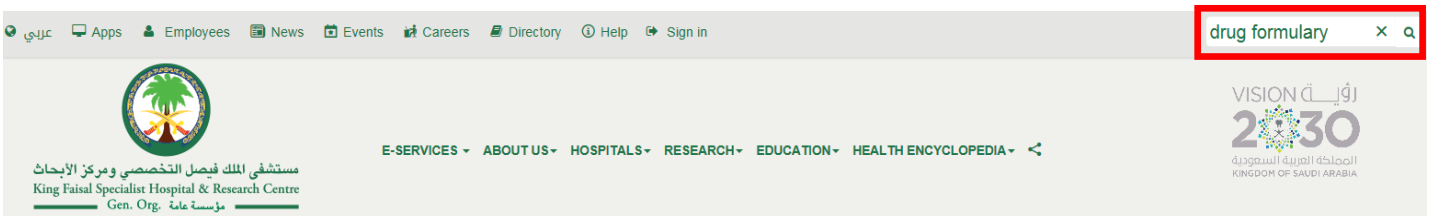
Skin Burn Risk with the Use of Topical Pain Relievers Containing Menthol, Methyl Salicylate or Capsaicin

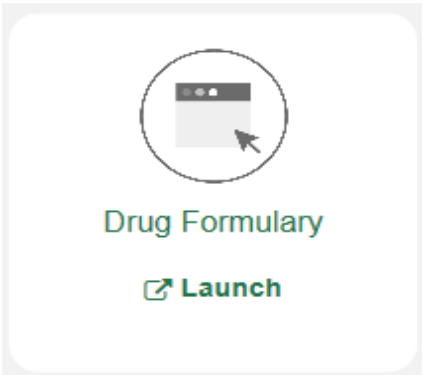
Health Canada is warning on the risk of rare but serious skin burns associated with the use of topical pain relievers containing menthol, methyl salicylate or capsaicin (e.g. Deep Heat®, Qutenza®, Zostrix®). As a result safety warnings have been added to the labels of these topical products. The review of the safety information provided by manufacturers identified over 100 additional international reports of serious burns linked to the use of topical products. The majority of these cases contained menthol alone or in combination with methyl salicylate. There were no cases of serious skin burns linked to the use of topical products containing methyl salicylate or capsaicin alone. There was only one case of serious skin burns linked to the use of a topical product containing methanol and methyl salicylate; however, the product was used inappropriately.

All drug safety alerts are communicated to the end-users of concern, as per the IPP MCO-CS-PCS-07-075: Dissemination and Action Related to Drug Safety Alerts at KFSHRC. For more info access IPP via Unified KFSHRC Portal.

Tip of the Issue

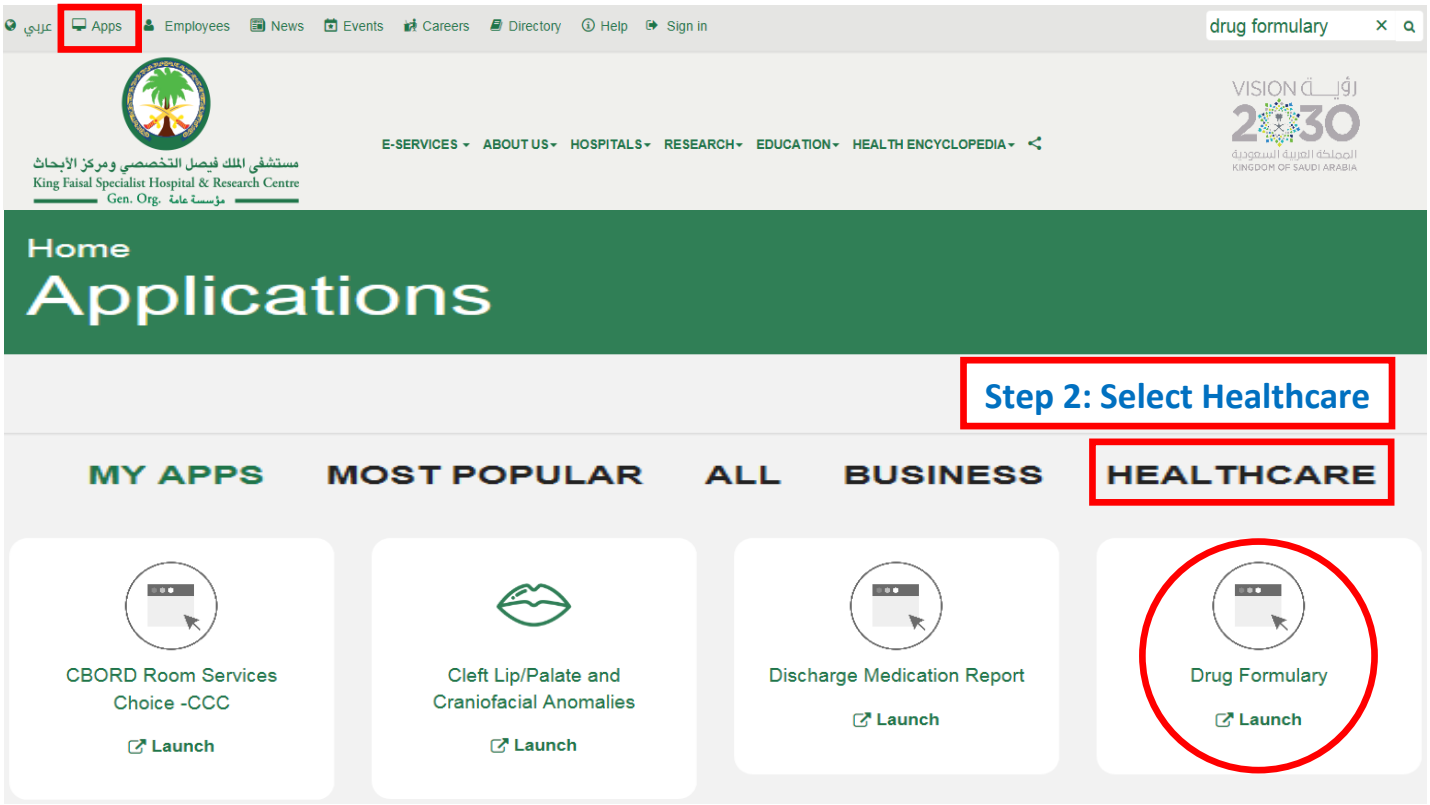
Navigating to Drug Formulary from New Unified KFSHRC Portal





Access the Drug Formulary using the search-bar (top right) and then launch the application

Step 1: Alternatively, select Apps



Step 2: Select Healthcare

KFSHRC hospital staff (Riyadh) can request for smartphone access to the KFSHRC Formulary through: druginformationcenter@kfshrc.edu.sa

Pharmacy Newsletter

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Continued...

The primary efficacy end point was a composite of death from cardiovascular causes, myocardial infarction or stroke. The secondary efficacy end point was death from any cause, myocardial infarction or stroke. The primary safety end point was TIMI major bleeding not related to coronary-artery bypass grafting (CABG). Combined rivaroxaban groups significantly reduced the primary efficacy end point compared with placebo (RRR=16 %, ARR= 1.8%, NNT= 55, p=0.008).

A significant improvement was shown for both the twice-daily 2.5 mg dose (reduction by RRR=16%, ARR= 1.6%, NNT= 62, p=0.02) and the twice-daily 5 mg dose (reduction by RRR=18%, ARR= 1.9, NNT= 52, p=0.03). The twice-daily 2.5 mg dose of rivaroxaban reduced the rates of death from cardiovascular causes by RRR=34 %, ARR= 1.4%, NNT= 71, p= 0.002, and from any cause by RRR=17%, ARR= 1.6, NNT= 62, p=0.002, a survival benefit that was not seen with the twice-daily 5 mg dose [95% CI 0.75-1.2]. Compared with placebo, rivaroxaban increased the rates of major bleeding not related to CABG by RRI=250%, ARI= 1.5%, NNH= 66, p<0.001 and intracranial hemorrhage by RRI=200%, ARI= 0.4%, NNH= 250, p=0.009, without a significant increase in fatal bleeding (0.3% vs 0.2%, p=0.66) or other adverse events, respectively. The twice-daily 2.5 mg dose resulted in fewer fatal bleeding events than the twice-daily 5 mg dose, respectively (0.1% vs 0.4%, p=0.04). According to the available evidence, rivaroxaban 2.5 mg twice daily reduced the risk of the composite end point of death from cardiovascular causes, myocardial infarction, major bleeding and intracranial hemorrhage.

In light of the available evidence, the European Medicines Agency (EMA) approved rivaroxaban 2.5 mg twice daily as part of a secondary-prevention strategy in ACS patients in March 2013. On the contrary, the US FDA denied the supplemental new drug application (sNDA) for the ACS indication for the third time in January 2014. Both regulatory bodies used the same evidence to support their decisions, albeit influenced by the differences in the nature and structure of their healthcare systems and pharmacoeconomic and cost-effective perspectives.

The healthcare system in the US has an established tertiary care infrastructure in comparison to Europe; where the strength of their healthcare system is in primary care. Therefore, disease prevention is the most common adopted approach in Europe and is well aligned with its socialized healthcare system. However, due to the US having a well-established tertiary care system, this has led to an increased number of interventional and diagnostic catheterization laboratories, resulting in a significantly higher cost for managing hemorrhagic stroke. The provision of healthcare is influenced by various factors, such as the main stakeholders. In the UK healthcare system this is the government, whereas in the US, it is the patient and health insurance.

Using the same evidence reviewed above, how does this apply to KFSHRC and Saudi Arabia in general? It is clear from the appraisal that the available and reviewed evidence indicates there is a benefit of using rivaroxaban in this group of patients, however, there is a significant increase in the risk of major bleeding. Our healthcare system adopts more of a socialized approach, with its limitations arising mainly due to an underdeveloped primary care infrastructure. We are advanced in tertiary care with the establishment of specialty hospitals and medical cities, however, the government is not investing enough in prevention strategies. A pharmco-economic approach adopted and implemented on the basis of cost of utilities and willingness to pay, would revolutionize the healthcare system in Saudi Arabia.

Access to tertiary care is restricted and our healthcare system is congested. Additionally, home healthcare services require further development and tailoring to suit the nature of our healthcare system. As a result, patients who suffer a hemorrhagic stroke may struggle to find beds in hospital and access to specialized healthcare.

Rivaroxaban use in ACS presents an insightful case and learning model on the appropriate application of the existing evidence. Despite the risk and benefit of a given intervention, an appraisal should not be carried without considering the nature and limitations any healthcare system poses. In addition, taking into consideration the economic status of the setting and patients preference.