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PHARMACY AND THERAPEUTICS NEWSLETTER

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In This Issue...

Changes to Formulary

Additions

Clinicians should review medication information prior to administering any unfamiliar medication. Resources include: VCH PDTM, Lexicomp®, or UpToDate®.

1. Rosuvastatin tablets (Crestor®)
- HMG-CoA reductase inhibitor (statin) antihyperlipidemic agent
- See Table 1 for revised Therapeutic Interchange for statins (page 2)

2. Naltrexone 50 mg tablets (Revia®)
- Opioid antagonist restricted to prescribing for alcohol use disorders

3. Acamprosate 333 mg delayed release tablets (Campral®)
- GABA-agonist/glutamate antagonist used to maintain abstinence from alcohol ingestion

4. Aripiprazole 300 mg, 400 mg long-acting injectable (Abilify Maintena®)
- Long-acting atypical antipsychotic agent

Deletions

1. Diazepam emulsion for injection (Diazemuls®)
- Discontinued by manufacturer

2. Mechlorethamine injection

3. Indigotindisulfonate injection (Indigo Carmine®)

4. Fibre 469 mg tablets
- Discontinued by manufacturer
- Alternative: Psyllium 525 mg capsules

5. Amino Acids 10% with Electrolytes (Travasol®)
- Discontinued by manufacturer
- Travasol 10% withOUT electrolytes will be used as the standard product for Parenteral Nutrition. The Parenteral Nutrition Pre-Printed Order has been revised accordingly.

Drug & Policy Revisions

1. LIDOCAINE INFUSIONS FOR PAIN MANAGEMENT
- Lidocaine infusions for management of post-operative or neuropathic pain are restricted to prescribing by POPS, PCU, and Dr. Negraeff (for spine patients on CP9).
- Nurses in post-surgical units can now administer lidocaine infusions for pain management.
- A baseline ECG only (ie. not continuous ECG monitoring) is required for:
  - ⇒ post-operative and spine patients for doses up to and including 2 mg/kg/hour for a duration of up to 72 hours
  - ⇒ patients in PCU for doses up to and including 3 mg/kg/hour, or IV Intermittent dosing

EDITORIAL STAFF:
Karen Shalansky, Pharm.D., FCSHP
Tim Lau, Pharm.D., FCSHP
Jane Day, B.Sc.(Pharm.), ACPR
Nilu Partovi, Pharm.D., FCSHP
Any comments, questions, or concerns with the content of the newsletter should be directed to the editors. Write to CSU Pharmaceutical Sciences Vancouver General Hospital, 855 W12th Ave, Vancouver BC V5Z 1M9, send a FAX to 604-875-5267 or email karen.shalansky@vch.ca

2. HYPERKALEMIA MANAGEMENT PRE-PRINTED ORDER (PPO #960)

- This PPO provides prescribers with a list of treatment options for the management of hyperkalemia.
- The PPO includes the correct route of administration for insulin, ie. **insulin must be given by the intravenous (IV) route** (NOT subcutaneously) when used for hyperkalemia.
- If prescribers opt to handwrite hyperkalemia treatment orders instead of using the PPO, it is recommended that the indication "For treatment of hyperkalemia" be included in the order. This heading will inform caregivers that the insulin is being used for treatment of hyperkalemia and is given by the IV route, rather than subcutaneously which is used for diabetes management.

3. BUPRENORPHINE-NALOXONE TABLETS (SUBOXONE®)

- On formulary without restrictions**.** Federal authorization to prescribe Suboxone® is no longer required.

4. FENTANYL SUBCUTANEOUS INJECTIONS

- Restricted to prescribing by Palliative Care Service on any nursing unit

5. THERAPEUTIC INTERCHANGE: STATINS

- As per the BCHA Provincial Formulary, all statins (other than pravastatin and rosuvastatin) are interchanged to atorvastatin as per Table 1.

Table 1. Statin Interchange to Atorvastatin

Drug Ordered			Drug Dispensed
Fluvastatin	**Lovastatin**	**Simvastatin**	**Atorvastatin**
20 mg	10 mg	5 mg	10 mg PO daily
40 mg	20 mg	10 mg	10 mg PO daily
80 mg	40 mg	20 mg	10 mg PO daily
-	80 mg	40 mg	20 mg PO daily
-	-	80 mg	40 mg PO daily

6. RITUXIMAB INDICATIONS

- Restriction for rituximab expanded to include:
  - ⇒ Adjunct therapy in heart transplantation for refractory biopsy proven antibody-mediated rejection (new criteria); or
  - ⇒ Indications outlined in the BCCA Benefit Drug List AND patients registered with BCCA; or
  - ⇒ Adjunct therapy in kidney transplantation for refractory biopsy-proven antibody-mediated rejection; or
  - ⇒ Indications outlined by BCPRA AND patients who are registered with BCPRA

Pharmacy Awards

Several members of the VA Pharmacy Staff have been honoured with the following awards:

- **Nilu Partovi, Pharm.D., FCSHP** received the *Above and Beyond Lifetime Achievement Award* from Fraser Health in appreciation for Nilu's hard work and dedication in providing the best care to her patients and continually trying to improve the provision of pharmacy services.
- **Tony Kiang, B.Sc. (Pharm), PhD and Wendy Cheng, B.Sc. (Pharm)** received the Canadian Society of Hospital Pharmacists (CSHP), BC Branch *Publication Award* for their research paper entitled "Predictive performance of the Winter-Tozer and derivative equations for estimating free phenytoin concentration". Co-authors were Penny Bring and Mary Ensom.
- **Karen Shalansky, Pharm.D., FCSHP** received the CSHP National *Specialties in Pharmacy Practice Award* for her research paper entitled "Creation of a Natural Health Products database for assessing safety in patients with chronic kidney disease and renal transplant". Co-authors were Sharon Leung, Judith Marin, Marianna Leung, and Puneet Vashisht.
- **Tim Lau, Pharm.D., FCSHP** received the CSHP National *Patient Care Enhancement Award* for his research paper entitled "Evaluation of a *Clostridium difficile* infection management policy at a major Canadian teaching hospital". Co-authors were Shirley Yeung, Janice Yeung, Leslie Forrester, Ted Steiner, William Bowie and Elizabeth Bryce.
- **Flora Yu, B.Sc. (Pharm)** received the CSHP, BC Branch *Residency Practice Award* for her research paper entitled "Risk Evaluation of antiPsychotic Agents used In the eldeRly in-patients (REPAIR)".
- **Karen Dahri, Pharm.D.** was awarded a grant from the UBC Teaching and Learning Enhancement Fund (TLEF) for her research entitled "Virtual Patients – Bridging the Gap Between the Classroom and Clinical Pharmacy Practice".

PENICILLIN AND BETA-LACTAM ALLERGIES Questions and Answers

Case: Piperacillin-tazobactam is prescribed for a patient who has a documented penicillin allergy. Is it safe to administer piperacillin-tazobactam to this patient?

1. What are penicillin and beta-lactam antibiotics?

Penicillins, cephalosporins, and carbapenems belong to the class of antibiotics known as beta-lactams (Table 3):

Table 3. Beta-Lactam Antibiotics

Penicillins	Cephalosporins	Carbapenems
amoxicillin	cephalexin	ertapenem
amoxicillin-clavulanate	cefazolin	imipenem-cilastatin
ampicillin	cefixime	meropenem
cloxacillin	cefotaxime	
penicillin	cefoxitin	
piperacillin-tazobactam (pip/taz)	cefuroxime	
	ceftriaxone	
	ceftazidime	

- Cephalosporins and carbapenems are similar to penicillins, but have different side structures.
- Adverse drug effects (including allergies) may occur in 1-10% of patients receiving penicillins and 1-3% of patients receiving cephalosporins.
- The frequency of anaphylactic reactions to penicillins is 0.01-0.02% with a fatality rate of 0.0015-0.02%.

2. If your patient has a penicillin allergy, how likely will they react to other beta-lactam antibiotics?

- Patients with a penicillin allergy may also have a reaction to:
  - ◊ Cephalosporins - incidence ~1 to 2.6%
  - ◊ Carbapenems - incidence ~1%
- Many patients who report a penicillin allergy do not actually have a true allergy.

3. What questions should I ask my patient who has a penicillin or beta-lactam allergy?

Table 4. Managing Beta-Lactam Allergies

i. What type of reaction occurred?	***Allergic reaction:*** - anaphylaxis (angioedema, hives, pruritus, difficulty breathing, and/ or hypotension) - rash	***Adverse drug effects/ intolerances:*** - headache - nausea, vomiting - stomach upset - diarrhea
ii. When did symptoms begin?	Anaphylaxis usually occurs within 1 hour to 24 hours after exposure.	
iii. How long ago did the reaction occur?	50% and 80% of penicillin allergic patients lose their sensitivity to penicillin in 5 years and 10 years, respectively; they may no longer be allergic.	
iv. Have you taken the same or a similar antibiotic since?	If the patient took the same/similar antibiotic at another time and did not have a reaction, they may safely take an antibiotic in the same class (i.e. penicillin, cephalosporin or carbapenem classes).	
v. Have you ever had a penicillin skin test by an allergist?	The penicillin skin test determines whether a patient will develop an "anaphylactic reaction" to penicillin class antibiotics.	

4. How should I manage my patient who has a beta-lactam allergy?

- Determine significance of beta-lactam allergy based on responses to the above questions.
- **<u>Penicillin allergy</u>**

  If patient has a history of an *allergic reaction* to any penicillin antibiotic:
  - ◊ <u>Avoid</u> all penicillin class antibiotics
  - ◊ May administer a cephalosporin, if the reaction to the penicillin was <u>not</u> anaphylactic
  - ◊ May administer a carbapenem, as the risk of cross-reactivity is low (with close monitoring)
- **<u>Cephalosporin allergy</u>**

  If patient has a history of an *allergic reaction* to any cephalosporin antibiotic:
  - ◊ <u>Avoid</u> cephalosporin class antibiotics.
  - ◊ <u>Avoid</u> giving a penicillin class antibiotic (see Table 3)
  - ◊ May administer a carbapenem, as the risk of cross-reactivity is low (with close monitoring)
- Refer to the "Antibiotic Cross-sensitivity Chart" at VHPharmsci.com website. Click on: *Formulary,* then *Prescribing Tools,* then *Antibiotic Cross Sensitivity Chart.*

Warfarin for Stroke Prophylaxis in Hemodialysis Patients with Non-valvular Atrial Fibrillation

Danielle Stacey Pharm.D., Karen Shalansky, Pharm.D.
Reviewed by Dr J Jastrzebski, Nephrology

Introduction:

The incidence of atrial fibrillation (AF) in hemodialysis (HD) patients ranges from 5.6-24.7%, with newly diagnosed AF occurring in 1 per 100 patient-years (range 0.5-3).[1-3] Risk factors associated with development of AF include advanced age, higher dialysate calcium, prosthetic heart valves, and valvular heart disease.[1] For the general population, clinical trial data and published guidelines support the use of warfarin for stroke prophylaxis in patients with AF, with initiation mainly guided by the use of risk stratification tools (eg. $CHADS_2$).[4,5] However, the role of anticoagulation for stroke prophylaxis in HD patients with AF remains controversial. Table 5 lists current major cardiovascular (CVS) guidelines outlining the management of these patients. Recommendations vary between not routinely prescribing oral anticoagulation[4] to prescribing warfarin only to those patients with a high $CHADS_2$-VASc score.[5]

Table 5. Cardiovascular Guidelines for Management of Atrial Fibrillation in HD Patients

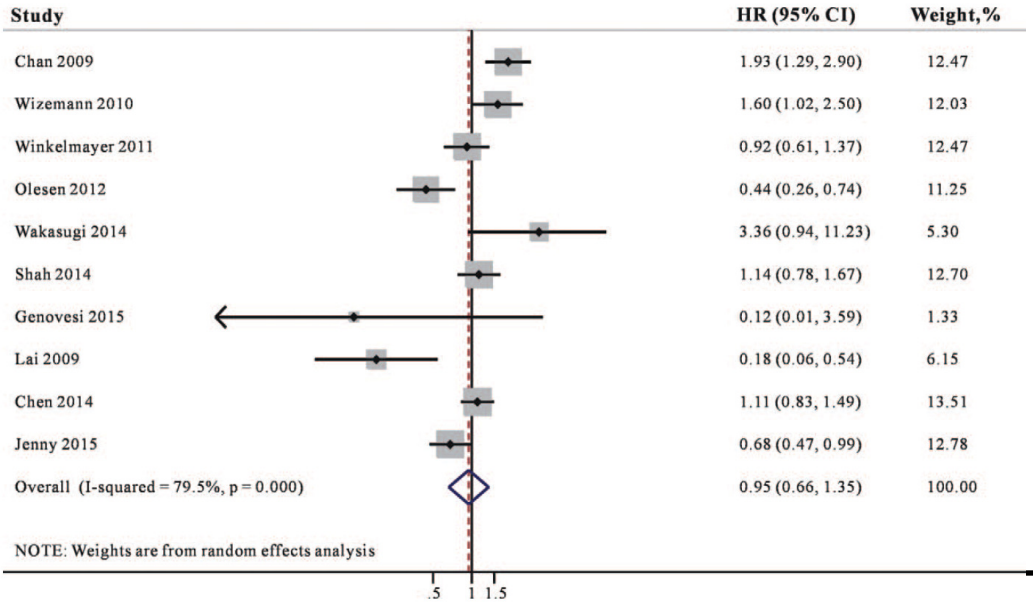
Guideline	Recommendation	Strength of Recommendation
Canadian Cardiovascular Society 2014[4]	eGFR<15 mL per minute (on dialysis): we suggest that such patients not routinely receive any oral anticoagulation	Conditional Recommendation, Low-Quality Evidence
American Heart Association 2014[5]	With $CHADS_2$-VASc score ≥ 2 and end-stage CKD (CrCl <15 mL/min) or on hemodialysis, it is reasonable to prescribe warfarin for oral anticoagulation	Class of Recommendation: IIa Level of Evidence: B
European Heart Rhythm Association 2015[6]	CKD (CrCl ≤ 15 mL/min): Vitamin K antagonists (VKA) are more suitable alternatives to NOAC therapy although the benefit of VKAs in such patients is not unequivocally proven. Careful individualized risk/benefit for VKA use is warranted.	Not reported

Efficacy and risk of warfarin for stroke prophylaxis in dialysis patients with AF

To date, there have been no prospective, randomized controlled trials conducted on warfarin use in HD patients with AF. There is conflicting evidence in individual, primarily retrospective cohort studies. Factors that may contribute to variability in outcomes include differences in baseline health and co-morbidities of patients, variability in outcome definitions, limited details about time within the therapeutic INR range, and variability in adjustment for confounders.

In 2015, Liu G *et al* published a meta-analysis of 10 observational studies (9 retrospective and 1 prospective cohort) evaluating the effectiveness of warfarin in a total of 25,407 dialysis patients with AF.[7] Compared to no treatment, warfarin was not associated with a lower risk of ischemic stroke (HR 0.95, 95% CI 0.66-1.35, Figure 1). In addition, warfarin use was associated with a 27% increased risk of bleeding (HR 1.27, 95% CI 1.04-1.54). A meta-regression analysis adjusting for potential sources of heterogeneity (age, sex, follow-up, study design, sample size, cardiac disease, diabetes, prior stroke) found that confounders did not affect the outcomes.

Figure 1. Combined estimate of Hazard Ratios (HR) of warfarin use associated with stroke risk[7]



The results by Liu *et al* are consistent with 2 other meta-analyses done in HD patients.[8,9] Three recent retrospective trials not included in the Liu *et al* meta-analysis also found no difference in incidence of stroke in HD patients with AF receiving warfarin compared to those who did not.[10-12] While 2 of these trials found no significant difference in bleeding rates[10,12], Wang *et al* found a significantly increased incidence of intracranial bleeds with the use of warfarin (n=59) vs no therapy (n=82) in HD patients followed for 4.4 +/- 2.5 years (6.8% vs 0, p=0.029).[11]

Warfarin safety concerns in HD patients

Bleeding Risk: The frequency of major bleeding events in HD patients without oral anticoagulation is reported to be between 0.8-11%, which increases to 3.1-54% per year with the addition of warfarin.[13-15] A history of GI bleed has been shown to be a strong predictor of a future serious bleed while on oral anticoagulation.[16] An analysis of 48,144 dialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS) found that bleed rates exceeded stroke rates by at least 2-fold in those with a previous GI bleed who were on oral anticoagulation.[16] Warfarin may also cause hemorrhagic stroke, and dialysis patients have been shown to have an increased risk of hemorrhagic stroke overall compared to the general population.[17]

Labile INRs: Warfarin requires regular monitoring to ensure the INR is within therapeutic range. Dialysis patients are known to have labile INRs and have been reported to have INRs within the therapeutic range less than 50% of the time.[18]

Drug interactions: There are numerous drug interactions with warfarin, including several antibiotics that are commonly prescribed for dialysis patients (e.g. ciprofloxacin, metronidazole, cotrimoxazole, clarithromycin, fluconazole) which cause increases in INR and thus, a potential increased risk of bleed.[19]

Application to clinical practice

Inconsistencies in the primary literature and mixed direction from current guidelines highlight that each HD patient with AF must be assessed individually for risks and benefits when considering the initiation of warfarin for stroke prophylaxis. In the general population, risk stratification is done through the use of $CHADS_2$, $CHADS_2VAS_c$, and HASBLED or ORBIE scores as dictated by current guidelines.[4-6] These tools have not been validated in the dialysis population. While analysis of DOPPS data found the $CHADS_2$ score was able to successfully stratify stroke risk in HD patients[16], studies have not shown that treatment with warfarin reduces stroke incidence.[7-12] As well, oral anticoagulation is associated with a higher bleed rate in this population.[7-9,13-15] Sood *et al* in 2009 created a risk-benefit table to stratify HD patients that could potentially benefit from warfarin therapy (Table 6).[20]

Conclusion

The use of warfarin in HD patients with AF is controversial due to the potential lack of benefit in stroke reduction and increased risk of severe bleed. Given the uncertainties in the net benefit, warfarin should only be considered in HD patients with high $CHADS_2$ scores, especially in those who have a previous history of TIA or stroke but no history of GI bleed or intracranial hemorrhage. In AF patients not suitable for oral anticoagulation, consideration should be given to the addition of an antiplatelet agent (e.g. ASA).

Table 6. Suggested Risk Stratification for Warfarin use in HD Patients with AF[20]

Risk Stratification	Description
Favours warfarin	Age > 75 years and risk factors (diabetes, hypertension, CHF) Previous transient ischemic attack (TIA) or stroke $CHADS_2$ score ≥ ORBI score by 2 points Prosthetic heart valve Mitral stenosis Known atrial thrombus
Favours no warfarin*	Age < 65 years with no risk factors (diabetes, hypertension, CHF) Uncontrolled Hypertension Concurrent antiplatelet agent use Previous hemorrhage or GI bleed** Calciphylaxis, history of or current Severe malnutrition Non-compliance Frequent falls

*Consider the use of antiplatelet agents if not receiving warfarin
**History of GI bleed found by author in a later study to significantly increase rate of subsequent bleed on warfarin (approaching 0.2 events/year)[16]

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