Warfarin and renal impairment nursing essay

Environment, Air

Author: Karishma KakH. BSc (2009)., BSc Pharm Candidate(2013)Conflict of interest: Past work term working in a pharmacist-managed anticoagulation clinic with warfarin. This manuscript is original, is not under consideration by another journal, has not been previously published, and has been approved by all authors. Focus: Focus will be placed on the specific risk associated with declining renal function and managing thromboembolic risk in the setting of atrial fibrillation with oral anticoagulation agents. Parenteral anticoagulants such as low molecular weight heparins although potentially an alternative for patients with moderate to severe CKD will not be discussed in this update because of lack of expert consensus on their use and their tendency to accumulate in renal dysfunction <1>. Stroke will be the primary clotting risk referred to in this update. Scope of this issueOver 15 million people in the United States are currently suffering from chronic kidney disease <1, 2>. Of this population, approx 530, 000 have end-stage renal disease and approximately 370, 000 receive maintenance dialysis <1>. Between 0. 4-1 percent of the American population suffers from atrial fibrillation, with the rates climbing upto 8% in the elderly above 80 years of age <1, 5>. Atrial fibrillation and CKD are independent risk factors for thromboembolic events. To complicate matters further, AF is common in CKD patients, especially those with end-stage renal disease <1>. For example, in patients with hemodialysis between 8 -34% of patients have a diagnosis of AF <4, 6>. Similarly, in patients with peritoneal dialysis, approximately 7% of the patients have a concurrent diagnosis of AF <1, 4, 6>. The rate of AF in this CKD population is 10-20 times higher than the rate of incidence of AF in the general population <1, 8, 9> Antithrombotic therapy typically used to reduce

risk of stroke in AF increases risk of bleeding. This risk is further potentiated by chronic kidney disease. The efficacy and safety of antithombotic agents have not been adequately studied in CKD patients with AF, especially the chronic end-stage renal disease patients, with or without dialysis. In addition, the risk of stroke in patients with AF and CKD increases as their renal function declines <1>. Of note, CKD is not included as a risk factor in the CHADs or CHADs2 score, partly because patients with CKD are rarely included in randomized control trials for treatment and outcomes. Similarly, most but not all studies also suggest an increase in the rates of both ischemic and hemorrhagic stroke in CKD patients because of AF. This increase in stroke risk is especially potentiated in dialysis patients with AF <1, 5>. The decision to anticoagulateThe need to carefully balance benefit of anticoagulation given high risk of stroke with the significantly increased risk of bleeding in CKD patients makes the decision to anticoagulate difficult. Like risk of stroke, worsening renal function is associated with an increase in the risk of bleeding. In a report of 578 warfarin treated patients with CKD, the risk of major hemorrhage was significantly greater in those with severe renal impairment defined as eGFR <30 mls/min vs. those with lesser degrees of impairment <9>. In CKD patients receiving hemodialysis and on warfarin, bleeding rates increased significantly and the use of warfarin was associated with close to a doubling in the rate of bleeding. Of note, most of this bleeding occurred in the gastrointestinal tract <1, 10, 11>. A Danish registry study further investigated the impact of CKD on the risk of bleeding in patients with AF. Risk of bleeding was found to be higher for patients requiring renal-replacement therapy in this study and for those patients with some degree

of CKD (not ESRD) <12> This increased risk of bleeding is thought to be potentiated by several different mechanisms such as impairment of normal platelet function by uremic toxins, altered von Willebrand factor, abnormal platelet arachidonic acid metabolism, reduction in intracellular ADP and serotonin, as well as an increase in the frequency of the need for invasive procedures in this population <1>. In CKD patients of all stages but especially those on hemodialysis, prothrombotic changes can also occur, making them more likely to coagulatate <1>. Literature on oral anticoagulants in CKD patientsThis section will compare warfarin with the newer oral anticoagulants on the market, namely dabigatran, apixaban and rivaroxaban and outline recommendations for patients with varying degrees of renal impairment.

Stage 3 CKD patients (eGFR 30-59 mls/min)

Older trials which compared warfarin to placebo, did not include patients with CKD, thus although this group is thought to receive similar anticoagulation benefit from warfarin, this benefit is only extrapolated <1>. Three trials have studied the safety and efficacy of oral antithrombotic agents in patients with Stage 3 CKD in subgroup analyses. Each of these large randomized trials, namely RE-LY, ARISTOTLE and ROCKET-AF studied the new anticoagulant agents dabigatran, abixaban and rivaroxaban respectively compared to treatment with adjusted dose warfarin to have INR’s between 2. 0-3. 0. The RE-LY trial found 150mg BID dose dabigatran superior to warfarin while the 110mg BID was noninferior to warfarin. The ARISTOTLE study found apixaban 5mg BID superior to warfarin and rivaroxaban at 15 mg daily was found to be non-inferior to warfarin.

ARISTOTLE and ROCKET-AF both found an increased incidence of clotting events in patients with stage 3 CKD in all groups <13, 14, 15>. The benefit of anticoagulation in patients with CKD and CHADs score 0 is weak but given the superiority of warfarin over aspirin in RCT's, oral anticoagulation is preferred over antiplatelets <1>. However, in some patients the increased risk of bleeding given renal dysfunction and anticoagulation may override the benefit and aspirin may be a suitable choice in these patients. In cases where anticoagulation is indicated (CHADs score > 0), apixaban/rivaroxaban or dabigatran are preferred over warfain in patients with Stage 3 CKD <1>

Stage 4 CKD patients (eGFR 15-29 mls/min

Since risk of bleeding and clotting increases with declining renal function and most patients with Stage 4 CKD are excluded from big randomized trials, recommendation for the decision to anticoagulate and choice of anticoagulation therapy vary from management in patients with Stage 3 CKD <1>. In these patients, risk of clotting is thought to exceed that of bleeding irrespective of CHADS2 score and although based on pharmacokinetics parameters, dabigatran 75 mg BID has been approved by the FDA for this population, its use in clinical practice is not recommended <1>. Warfarin is the agent recommended for anticoagulation in this agent because of its historical use and proven efficacy/safety. Aspirin is not thought to provide sufficient protection in these patients. However patients with CKD stage 4 on warfarin will need to be educated about risk of bleeding and the need to hold anticoagulation in the event of a bleed <1>.

Stage 5 CKD: End stage renal disease (eGFR less than 15 mls/min) +AF

Stage 5 CKD patients are at an especially increased risk of both bleeding and clotting, rarely studied in clinical trials and have potentially difficulty in gaining access to veins for regular INR monitoring <1>. The results of the few studies looking at warfarin use in this population have yielded mixed results. The results of two retrospective studies of hemodialysis patients with AF demonstrated a potential for an increased risk of stroke in the warfarin group vs. placebo in one study, with the risk increased nearly two fold in the other <1, 16, 17>. Another report from the US Renal Data System comparing survival in two groups of ESRD patients, one receiving mechanical heart valves and oral anticoagulation and another receiving tissue valves and likely no oral anticoagulation found no difference in survival rates <1, 18>. Anticoagulation with warfarin is recommended in patients with a CHADS2 score of equal to or greater than 1. For patients with a CHADS2 score of 0, recommendations on anticoagulation are mixed. It may be beneficial for carefully selected patients based on clinical judgement <1>.

Warfarin and Renal impairment

Although warfarin is hepatically cleared, studies have found an association with increased bleeding and labile INR’s in patients with declining renal impairment. A study with 565 explored the relationship between renal impairment and warfarin dosing requirement. Patients in this study were stratified by baseline renal function (eGFR ≥60, 30 to 59, or less than 30 mL/min per 1. 73 m2) <1, 9, 10>. Patients with severe CKD had significantly lower warfarin dosage requirements and lower INR’s in range compared to

those with lesser degrees of renal impairment. Based on this study and several others, a lower starting dose of 2. 5 mg x first two days of initiating warfarin is recommended for patients with CKD and eGFR of less than 30 mls/min <1>. Clinical Bottom-lineCKD Stage 3: Anticoagulation with rivaroxaban or dabigatran over warfarin in patients with CHADS2 score equal to or greater than 1CKD Stage 4: Chronic anticoagulation should be considered in patients with AF irrespective of their CHADS2 score. Warfarin is the chosen agent in this populationCKD Stage 5: Warfarin is recommended in those with CHADS2 score of equal to or greater than 1 without a very high risk of bleeding, the decision to anticoagulate those with a CHADS2 score of 0 is unclear. A starting dose of warfarin 2. 5 mg daily x 2 days for patients with AF and CKD stage 3 or lower is recommended.