assessment of AMI 100% of the time (kappa = 1) in the no positive phenotype stratum. There was 72% agreement in the strata in which 1 to 3 phenotypes were positive (kappa = 0.51), and 78% agreement in the strata in which all phenotypes were positive (kappa = 0.42). When assessing which components of the UDMI were most strongly associated with disagreements, we found that cardiac biomarker changes and symptoms of ischemia were most strongly associated with disagreements compared with electrocardiogram changes, imaging evidence, or cardiac death/autopsy findings of AMI.

Of the 70 AMIs by chart review, all algorithms were positive for 19 (27%) encounters, and 1 to 3 algorithms were positive for 51 (73%). **Table 1** presents the sensitivity/specificity of each algorithm for AMI identification compared with the UDMI.

In summary, the CMS Chronic Conditions Warehouse was found to have the highest sensitivity and a high specificity via assessment of inpatient claims with the International Classification of Diseases, Ninth Revision codes of 410.X1 in the first or second position for discharge or final diagnosis. The high sensitivity supports its use to rule out an AMI in those with negative administrative data, and the high specificity rules in an AMI event in those with positive administrative data. Importantly, these findings were observed in a single-center analysis of Durham County residents. We did not specifically document details related to completeness of electrocardiography data or subsequent revascularization.

Importantly, prior analyses demonstrated that classification of nonfatal events in routinely-recorded EHR-type data is imperfect (2). EHRs are heterogeneous, and data elements are inconsistently defined (3). The complexity of the healthcare system can affect the utility of the EHR for outcome ascertainment, as patients receive care from multiple providers and institutions. An improved understanding of how to make administrative algorithms more accurate would facilitate outcomes research. Future research is needed to validate these observations and investigate other endpoints including revascularization, stroke, and heart failure events.

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Pharmacokinetics and Pharmacodynamics of Dabigatran 75 mg b.i.d. in Patients With Severe Chronic Kidney Disease

Dabigatran etexilate (dabigatran) is a direct oral thrombin inhibitor approved for the prevention of ischemic stroke in patients with nonvalvular atrial fibrillation. Dabigatran has ~80% renal excretion, so patients with creatinine clearance (CrCl) <30 ml/min were excluded from phase 3 studies. On the basis of

post hoc pharmacokinetic (PK) modeling (1,2), the U.S. Food and Drug Administration approved a lower dose of 75 mg twice daily (b.i.d.) for patients with severe chronic kidney disease (CKD) (CrCl 15 to 30 ml/min). This study prospectively investigates the PK and pharmacodynamics of dabigatran 75 mg b.i.d. in patients with severe CKD and compares the observed PK data with predictions from 2 PK models (1,3).

We performed an open-label, single-center study in which patients received dabigatran 75 mg b.i.d. for 7.5 days (15 administrations) followed by 4-day washout. Inclusion criteria were stable CrCl (Cockcroft-Gault formula) between 15 to 30 ml/min over the last 3 months (change in creatinine <20%), age <18 years, and treatment with vitamin K antagonists (VKA) or aspirin (any indication). Important exclusion criteria were: >1 platelet aggregation inhibitor, uncontrolled hypertension, previous hemorrhagic stroke, or gastrointestinal bleeding.

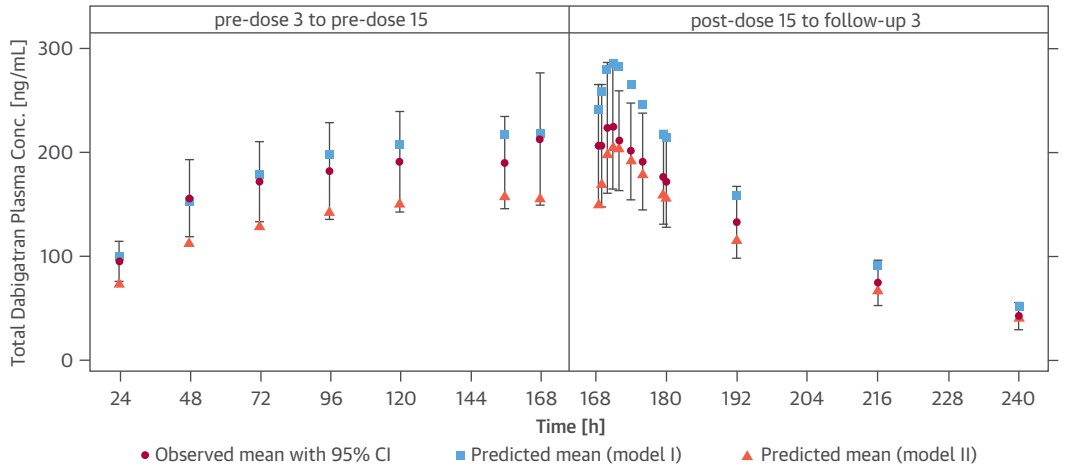
Patients stopped aspirin or VKA treatment 5 to 7 days prior to the first study day. Patients on VKA treatment received the first dabigatran dose when prothrombin time-international normalized ratio <2.0. Blood samples were collected every 24 h, with full profiles obtained over the dosing interval on the first and last day of dabigatran intake.

Primary endpoints were dabigatran plasma PK parameters: $C_{max,ss}$ (maximum measured concentration in plasma at steady-state) and $AUC_{\tau,ss}$ (area under the concentration-time curve at steady-state, over an interval τ of 12 h). A graphical comparison was made between the means of observed and predicted total dabigatran concentrations (on the basis of 2 PK models) (1,3). The effect of dabigatran on blood coagulation was assessed using activated partial thromboplastin time, ecarin clotting time, and diluted thrombin time.

In 2013, 16 patients entered the study: 11 were taking aspirin and 5 taking VKA pre-treatment. Mean age was 73 ± 8 years, and 81.3% were male. Mean CrCl was 22.8 ml/min (range 15.0 to 33.0 ml/min). One patient's data was excluded due to CrCl miscalculation (33 ml/min). Patients took their trial medication as planned, although 1 patient forgot her evening dose on day 3. No cardiovascular or major bleeding events occurred.

Total dabigatran PK values expressed as median (10th to 90th percentiles) were as follows: C_{max} (maximum concentration of the analyte in plasma measured after the first dose administration) 59.2 ng/ml (30.8 to 91.9 ng/ml), $C_{pre,ss,15}$ (pre-dose plasma concentration of the analyte at steady state immediately before administration of the last [15th] dose) 176 ng/ml (99.3 to 359.0 ng/ml), $C_{max,ss}$ 215 ng/ml (116 to 365 ng/ml), $AUC_{\tau,ss}$ 2,270 ng·h/ml (1,160 to 3,800 ng·h/ml), and $t_{1/2,ss}$ (terminal half-life at steady state for the last dose administration) 27.8 h (25.5 to 31.7 h). We compared the observed mean concentration-time profile of total dabigatran with predicted values of 2 PK models (**Figure 1**).

FIGURE 1 Observed (Mean and 95% CI) and Predicted (Mean) Total Dabigatran Plasma Concentration Profiles Following 75 mg b.i.d. in Patients With Severe CKD



Predictions marked "model I" were derived from a model (1) on the basis of mean data from severe chronic kidney disease (CKD) patients participating in a single-dose dabigatran trial. Predictions marked "model II" were derived from a model (3) on the basis of data from the RE-LY (Dabigatran versus Warfarin in Patients with Atrial Fibrillation) trial. CI = confidence interval.

Model I predicts the observed pre-dose means adequately, but tends to overpredict the peak. Model II tends to underpredict the pre-dose means, but adequately describes the peak. Deviations lie within the range of uncertainty. Furthermore, all observed means are within the concentration range intended at the time of selection of the 75-mg b.i.d. dose.

Mean baseline aPTT was 28.7 ± 3.2 s; 56.2 ± 7.3 s was the maximum at steady-state. For dTT, these values were 30.1 ± 2.5 s and 65.5 ± 16.9 s, respectively. Maximum ECT values at baseline and steady-state were 37.4 ± 2.9 s and 123.0 ± 35.7 s, respectively.

Our study has 2 main findings. First, the 75-mg b.i.d. dabigatran regimen results in mean steady-state drug exposure in patients with stable severe CKD comparable to predicted exposure, confirming the outcomes of the PK models used to establish the U.S. Food and Drug Administration–approved dabigatran dose for this population (1,3). Second, our results indicate that the 75-mg b.i.d. dabigatran regimen does not result in drug accumulation beyond 5 days of treatment.

Our results should be interpreted with certain considerations. Included patients had varying indications for either aspirin or VKA use. Moreover, our study was not designed to study the efficacy and safety of dabigatran in patients with severe CKD.

In conclusion, our study findings indicate that the dabigatran 75-mg b.i.d. regimen achieves predicted drug exposure in patients with severe CKD without accumulation beyond 5 days of treatment. Future clinical studies are needed to study the clinical efficacy and safety of dabigatran relative to warfarin in this specific patient population.

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Underutilization of Anticoagulation for Stroke Prevention in Atrial Fibrillation

Failure to prevent stroke in patients with atrial fibrillation (AF) has become increasingly important for patient safety and quality of care. Therefore, we conducted a multicenter, outpatient clinic, retrospective cohort analysis using data abstracted through our electronic health record between March 2013 and March 2014.

The patient cohort was identified by a query to the Partners Quality Data Warehouse. Patients with modifiers to the problem list entry of AF, such as "history of," were excluded. Patients with valvular heart disease were included. Clinical characteristics, CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65 to 74 years, sex category), and HAS-BLED (Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INRs, Elderly, Drugs or alcohol) scores, guideline adherence, and 90-day outcomes (all-cause mortality, stroke, systemic embolic events, and bleeding) were determined by a web-based decision support tool.

A total of 5,062 patients were captured by our electronic data query and satisfied the inclusion