Effect of Chronic Kidney Disease on Warfarin Management in a Pharmacist-Managed Anticoagulation Clinic

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ABSTRACT
BACKGROUND: There is growing evidence that kidney disease affects heparically cleared drugs. Accordingly, we hypothesized that chronic kidney disease (CKD) would disrupt anticoagulation of warfarin-treated patients and thereby increase the amount of management required to maintain appropriate anticoagulation. Specifically, we anticipated that more dose manipulations (both dose changes and transient dose adjustments) and shorter times between scheduled clinic visits would be required for anticoagulation patients with CKD.

OBJECTIVES: To determine how CKD affected warfarin maintenance dose, anticoagulation stability, the proportion of clinic visits that necessitated a dose manipulation (either a change in the prescribed weekly dose or a transient dose adjustment), and the length of time between scheduled visits in 2 pharmacist-managed anticoagulation clinics.

METHODS: Our retrospective, cohort chart review investigated warfarin response in anticoagulation clinic patients. From the clinic database of patients with an international normalized ratio (INR) target range of 2.0-3.0, we matched 20 of 24 patients with CKD (estimated creatinine clearance < 60 mL per minute) to 20 comparison group patients (estimated creatinine clearance > 60 mL per minute) based on parameters demonstrated to affect warfarin dose: ethnicity, gender, age, body surface area, and simvastatin use. We calculated the average weekly dose used to maintain target INR (assessment period range = 116-1,408 days). To evaluate anticoagulation stability and patient management, we quantified several parameters, including the percentage of total time in therapeutic range, the proportion of clinic visits that required a dose change, and the time between scheduled visits. We compared group means using t-tests, and categorical data were compared using Fisher’s exact test.

RESULTS: Our population was predominantly female (75%) and of African ancestry (95%); average age 60 years. Patients with CKD required a 24% lower dose than the comparison group (mean [SD] = 35.9 [10.7] vs. 47.0 [11.2] mg per week, P=0.003) and spent less time in therapeutic range (62% [18%] vs. 74% [14%], P=0.021). Furthermore, patients with CKD required increased clinic management versus the comparison group, as indicated by a significantly higher proportion of clinic visits at which dose changes occurred (22% vs. 12%, P<0.001) and a decreased time between scheduled visits (mean [SD] of 16.0 [3.2] days vs. 19.7 [3.4] days, respectively, P=0.001).

CONCLUSIONS: CKD was associated with both decreased warfarin maintenance dose and decreased anticoagulation stability which, in turn, required more frequent and intensive anticoagulation clinic management.

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What is already known about this subject
• Lower warfarin doses are required to maintain therapeutic anticoagulation in patients with moderate (approximately 10% dose reduction) and severe kidney disease (approximately 20% reduction).
• Patients with severe kidney disease have fewer international normalized ratio measurements within their target range (approximately 40% of the values) and are at increased risk of over-anticoagulation (hazard ratio 1.49 vs. patients with no renal dysfunction)
• However, no information is available on how often such patients are monitored and how often their warfarin dose requires manipulation.

What this study adds
• In a small matched-sample analysis conducted in 2 pharmacist-managed anticoagulation clinics, even patients with moderate kidney disease exhibited markedly reduced anticoagulation stability; their time in therapeutic range averaged 62% versus 74% for patients with an estimated creatinine clearance more than 60 mL per minute.
• More intensive anticoagulation clinic management is required for patients with moderate kidney disease than for matched comparison group patients; dose changes were required almost twice as often (22% vs. 12% of visits, respectively), and the mean time between scheduled visits was shorter (16.0 vs. 19.7 days, respectively).

Despite more than 50 years of warfarin use, the factors that affect patients’ response to this therapy have not been completely identified. In fact, even with the recent appreciation that genetics can play a role, it has been estimated that approximately 40%-45% of observed interpatient response variability remains unaccounted for.12 Such uncertainties in response contribute to warfarin’s underuse in some patients who could benefit from anticoagulation and have provided an impetus for the development of alternative anticoagulants. Nevertheless, warfarin’s role as an anticoagulant is unlikely to be replaced entirely, and therefore identification and characterization of factors that influence dose are still required.
The decision to start a patient on warfarin or to continue with warfarin therapy versus making a switch to one of the new anticoagulants is an important and difficult one not only in terms of safety and cost, but also in terms of the practical aspects of maintaining adequate anticoagulation. Recent analysis indicates that warfarin is a cost-effective therapy when anticoagulation stability is well controlled. Furthermore, good anticoagulation control with warfarin is also associated with increased safety. Therefore, approaches to improve anticoagulation control in warfarin-treated patients have potential to have an impact on managed care.

The potential effect of chronic kidney disease (CKD) on nonkidney drug clearance and metabolism has garnered increased attention and prompted assessment of warfarin dosing in patients with CKD. Indeed, there is emerging evidence that such patients require reduced warfarin maintenance doses and, with severe disease, exhibit impaired anticoagulation control. Specifically, patients with severe kidney disease required an approximate 20% reduction in warfarin dose and yet had fewer international normalized ratio (INR) measurements within the target range (approximately 40%) and were at increased risk of over-anticoagulation (hazard ratio 1.49) versus patients with no renal dysfunction. Our aim was to extend these initial observations and quantify the effect of moderate CKD on (a) warfarin maintenance dose, (b) anticoagulation stability, and, especially (c) the proportion of anticoagulation clinic visits that required a dose manipulation and the length of time between scheduled clinic visits.

**Description of the Anticoagulation Management Services**

We collected data from 2 anticoagulation clinics at the Detroit Medical Center: the Harper University Hospital Anticoagulation Clinic and The Rosa Parks Senior Health Center. The former clinic operates with 2.5 pharmacist full-time equivalent (FTE) positions, supported by 2 pharmacy technician FTEs, and has an enrollment of approximately 500 patients with approximately 8,000 clinic visits per year. The latter clinic operates with a 0.3 FTE pharmacist position and has an enrollment of approximately 50 patients with approximately 750 visits per year. At both clinics, pharmacists perform drug therapy management under a collaborative practice agreement with physician oversight. The collaborative practice agreement provides guidelines under which pharmacists evaluate and adjust warfarin therapy and order laboratory tests, and describes the circumstances in which the physician must be contacted. However, pharmacists use their own clinical judgment in making individual warfarin dosing and follow-up evaluation decisions; there is no mandated protocol for either activity in the collaborative practice agreement.

**Methods**

The protocol was approved by the Wayne State University Human Investigation Committee and received authorization from the Detroit Medical Center. Using a retrospective, observational, cohort chart review, we examined the electronic records of current and former patients at both pharmacist-managed anticoagulation clinics. We selected patients from a database compiled for a previous study. This database included patients who had an INR target range of 2.0-3.0, were older than 18 years, and attended the clinic for more than 3 months, and had at least 8 clinic visits after achievement of therapeutic anticoagulation (defined as 2 consecutive INRs within the target range). Patients treated with amiodarone or who required dialysis were excluded from the database. Data were collected, depending upon each patient’s enrollment in the clinic, from April 2005 to February 2009. Patients were matched on parameters demonstrated to affect warfarin dose: ethnicity, gender, age, body surface area, and simvastatin use.

Figure 1: Patient Selection Flowchart

![Flowchart](https://example.com/flowchart.png)

- **CKD Group**
  - 219 patients in database
  - 83 patients excluded: older than 70 years
  - 136 patients
    - 24 patients with eCrCl <60 mL per min
    - 112 patients with eCrCl >60 mL per min
    - 4 unmatched
    - 20 matched pairs

- **Comparison Group**
  - 219 patients in database
  - 83 patients excluded: older than 70 years
  - 136 patients
    - 24 patients with eCrCl <60 mL per min
    - 112 patients with eCrCl >60 mL per min
    - 4 unmatched
    - 20 matched pairs

*The database comprised patients from 2 pharmacist-managed anticoagulation clinics. All patients included in the database were older than 18 years, had an INR target range of 2.0-3.0, had attended the clinic for more than 3 months, and had at least 8 clinic visits after achievement of therapeutic anticoagulation (defined as 2 consecutive INRs within the target range). Patients treated with amiodarone or who required dialysis were excluded from the database. Data were collected, depending upon each patient’s enrollment in the clinic, from April 2005 to February 2009. Patients were matched on parameters demonstrated to affect warfarin dose: ethnicity, gender, age, body surface area, and simvastatin use. CKD=chronic kidney disease; eCrCl=estimated creatinine clearance; INR=international normalized ratio, ml. per min=milliliters per minute.
per minute (mL per min, calculated using the Cockcroft-Gault equation)—and a comparison group with eCrCl more than 60 mL per min. For each patient, eCrCl was calculated as the average of all outpatient measurements taken (median 4 measurements; interquartile range 3-7) during the assessment period (range = 116-1,408 days).

To maximize our ability to detect effects on warfarin dose, we matched each patient with CKD to a single comparison group patient based on parameters documented in a previous study to influence warfarin dose; specifically, ethnicity, gender, age, body surface area (BSA), and simvastatin use. Some of these (ethnicity, gender, and simvastatin use), we matched exactly, while age and BSA were matched as closely as possible. The median age difference (interquartile range) between the matched pairs was 4 (1-7) years, while the median BSA difference (interquartile range) was 0.13 (0.05-0.24) square meters (m²). Furthermore, because these 2 parameters have opposite effects on dose (dose decreases with age but increases with BSA), if the patient with CKD was slightly older than potential comparison group matches, we attempted to identify a comparison group patient with a lower BSA (or vice versa) so the 2 influences would offset. Patient matches were conducted without knowledge of the warfarin dose. In addition, we recorded each patient's indication for warfarin therapy and history of tobacco and alcohol use. The weekly average servings of green leafy vegetables (used as a proxy for vitamin K consumption) was also recorded at each clinic visit, as was use of medications categorized to have highly probable major inducer or inhibitor interactions with warfarin (listed in Holbrook et al., 2005).

Our first goal was to determine the average weekly warfarin dose required to maintain contraceptive INR. Therefore, we recorded the weekly warfarin dose prescribed at each clinic visit and then calculated the average dose over all visits recorded in the electronic record. Transient dose adjustments, defined as a temporary change (1-3 days in duration) in dose followed by a return to the previously prescribed weekly dose, were excluded from the weekly dosage calculation. Data were, depending upon each patient's enrollment in the clinic, collected from the time when the clinics' electronic medical records began (April 2005) until February 2009.

To determine if CKD affected anticoagulation stability, we recorded the INR measured at each visit. The following parameters were then calculated for each patient: (a) the total time in therapeutic range (TTR; calculated using the linear interpolation method), expressed as a percentage of observation time; (b) the proportion of visits with INRs within target range; and (c) the proportion of visits with INRs less than 2.0 and the proportion of visits with INRs more than 4.0.

We also assessed the effect of CKD on clinic management of the patients. To evaluate this, we determined the proportion of visits that required (a) a change in the weekly warfarin dose, (b) a transient dose adjustment (as defined above), and (c) any dose manipulation (a dose change or a dose adjustment). Decisions to manipulate the dose were based on the pharmacist's judgment. We also calculated the average length of time between scheduled visits and the average number of visits per year.

### Statistical Analysis

Data are presented as mean (SD) except where indicated. We compared group means using t-tests. Categorical data were compared using Fisher’s exact test and, when multiple comparisons were made, a Bonferroni correction was applied. Statistical analysis was performed using GraphPad PRISM 5.0 (GraphPad Software, Inc., La Jolla, CA), and differences were considered significant when $P<0.05$.

### Results

Of the 136 eligible patients in the database (83 were excluded because they were older than 70 years of age), 24 had CKD (Figure 1). We found matches for 20 of these patients. Our study cohort was composed predominantly of females of African ancestry, which reflected the overall patient population of the clinics. Of the 4 patients for whom suitable matches could not be found, 3 were of European ancestry and hence had fewer possible matches. As anticipated, because of the effort to match patients’ potential warfarin dose-influencing characteristics and demographics, there were no between-group differences in these parameters (Table 1). In addition, the groups were well matched for vitamin K consumption, assessment time, number of clinic visits, and the number of warfarin inducer or inhibitor

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**TABLE 1 Patient Demographics and Warfarin Dose-Influencing Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Comparison Group n = 20</th>
<th>CKD n = 20</th>
<th>P Value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender female</td>
<td>95 (19)</td>
<td>95 (19)</td>
<td>—</td>
</tr>
<tr>
<td>Gender male</td>
<td>75 (15)</td>
<td>75 (15)</td>
<td>—</td>
</tr>
<tr>
<td>Age (years)</td>
<td>59 [7]</td>
<td>61 [6]</td>
<td>0.300</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>2.00 [0.19]</td>
<td>2.03 [0.19]</td>
<td>0.616</td>
</tr>
<tr>
<td>Assessment period (days)</td>
<td>580 [231]</td>
<td>509 [417]</td>
<td>0.508</td>
</tr>
<tr>
<td>Clinic visits</td>
<td>30 [13]</td>
<td>30 [22]</td>
<td>0.993</td>
</tr>
<tr>
<td>Creatinine clearance (mL per min)</td>
<td>89 [13]</td>
<td>47 [9]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Warfarin inducers per patient</td>
<td>0.10 [0.31]</td>
<td>0.05 [0.22]</td>
<td>0.560</td>
</tr>
<tr>
<td>Warfarin inhibitors per patient</td>
<td>0.35 [0.49]</td>
<td>0.50 [0.51]</td>
<td>0.350</td>
</tr>
</tbody>
</table>

<sup>a</sup>Chronic kidney disease was defined as estimated creatinine clearance ≤60 mL per min. The comparison group had an estimated creatinine clearance >60 mL per min. <sup>b</sup>P values calculated using t-tests.

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GLV = green leafy vegetables—used as a proxy for vitamin K consumption; m² = square meters; mL per min = milliliters per minute; SD = standard deviation.
Effect of Chronic Kidney Disease on Warfarin Management in a Pharmacist-Managed Anticoagulation Clinic

**TABLE 2** Patient Comorbidities and Use of Tobacco and Alcohol

<table>
<thead>
<tr>
<th>Characteristics a</th>
<th>Comparison Group n = 20</th>
<th>CKD b n = 20</th>
<th>P Value b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>% (n)</td>
<td>% (n)</td>
<td>1.000</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>30 (6)</td>
<td>40 (8)</td>
<td>0.741</td>
</tr>
<tr>
<td>Heart failure</td>
<td>15 (3)</td>
<td>45 (9)</td>
<td>0.082</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>25 (5)</td>
<td>40 (8)</td>
<td>0.501</td>
</tr>
<tr>
<td>COPD</td>
<td>10 (2)</td>
<td>15 (3)</td>
<td>1.000</td>
</tr>
<tr>
<td>CVD</td>
<td>10 (2)</td>
<td>30 (6)</td>
<td>0.235</td>
</tr>
<tr>
<td>Liver disease</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>5 (1)</td>
<td>10 (2)</td>
<td>1.000</td>
</tr>
<tr>
<td>History of tobacco use</td>
<td>30 (6)</td>
<td>25 (5)</td>
<td>1.000</td>
</tr>
<tr>
<td>History of alcohol use</td>
<td>25 (5)</td>
<td>25 (5)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

aChronic kidney disease was defined as estimated creatinine clearance < 60 mL per min. The comparison group had an estimated creatinine clearance > 60 mL per min.

bP values calculated using Fisher’s exact test.

Patient characteristics were measured from the time when the electronic medical records began in the 2 study clinics (April 2005) through February 2009, depending on each patient’s clinic enrollment date.

CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CVD = cerebrovascular disease; mL per min = milliliters per minute.

Warfarin Dose and Anticoagulation Stability

Patients with CKD required, on average, a 24% lower weekly warfarin dose than comparison group patients (mean [SD] 35.9 [10.7] milligrams [mg] vs. 47.0 [11.2] mg, P = 0.003; data not illustrated).

TTR was lower in patients with CKD (mean [SD] 62% [18%] vs. 74% [14%], P = 0.021), consistent with decreased anticoagulation stability (Figure 2). We found a lower proportion of INR measurements within the 2.0-3.0 target range for patients with CKD versus the comparison group (352 of 598 [59%] vs. 408 of 598 [68%], P < 0.001). There was no statistically significant difference in the proportion of visits with subtherapeutic (< 2.0) INRs (CKD 107 [18%] vs. comparison group 97 [16%]). However, there was a 4-fold increase in the number of INRs greater than 4.0 in patients with CKD (40 [7%] vs. 10 [2%], P < 0.001).

Patient Management

The observed decrease in anticoagulation stability had consequences for the management of patients with CKD. Specifically, patients with CKD had almost twice as many visits with a change in the prescribed weekly dose than the comparison group (22% vs. 12%, P < 0.001; Figure 3). Although there was no significant difference in the proportion of visits with transient dose adjustments alone (CKD 22% vs. comparison group 20%, P = 0.571), patients with CKD required some type of dose manipulation at 44% of their clinic visits versus 33% of the visits for the comparison group (P < 0.001). In addition, patients with CKD had a shorter time between scheduled visits than the comparison group (mean [SD] 16.0 [3.2] vs. 19.7 [3.4] days, P = 0.001). This reduction of approximately one-half week between visits corresponded to an additional 4.5 clinic visits per patient-year for patients with CKD versus the comparison group (23.6 [4.6] vs. 19.1 [3.3], P < 0.001; data not shown in figure).
Kidney Disease, Anticoagulation Stability, and the Effect on Patient Management

Kidney disease was associated with decreased anticoagulation stability, indicated by the significant decrease in TTR and the proportion of visits at which INR was within the target range versus the comparison group. The latter decrease was consistent with published results, however, none of the previous studies examined changes in TTR. Our comparison and CKD groups’ TTRs (74% and 62%, respectively) were greater than or comparable to averages reported in a meta-analysis of clinic (64%) and community-based (57%) management. However, when we analyzed data from that meta-analysis, we found a correlation (r=0.386, P=0.005; data not shown) between TTR and follow-up time (the longer the follow-up, the higher the TTR) in cohorts followed for more than 3 months and for which the linear interpolation method for TTR calculation was used (i.e., the same criteria we employed). The average observation period in the current study (approximately 18 months) was longer than those of the majority of the studies included in the meta-analysis and may therefore partly explain our relatively high TTR values. Nevertheless, there was no doubt that patients with moderate CKD exhibited less anticoagulation stability than our comparison group, and moreover, this reduction had consequences for their management.

Another important aspect of anticoagulation stability not assessed in previous studies of CKD was the effect on patient dose. For patients with CKD, nonetheless, they emphasized that estimating the magnitude of the dose effects would be difficult without empirical data. The first data to confirm reduction in required warfarin dose for patients with CKD were obtained by Limdi et al. (2009). Their study compared warfarin dose, anticoagulation control, and hemorrhagic events in patients with mild or no CKD, patients with moderate CKD (estimated glomerular filtration rate [eGFR] of 30-59 mL per min per 1.73 m²), and those with severe disease (eGFR less than 30 mL per min per 1.73 m²). Patients with severe CKD required a lower dose (approximately 20% less than that of patients with no or mild disease), had fewer clinic visits with INR values within the target range, and were at increased bleeding risk. A follow-up study from the same group (Limdi et al., 2010) reported that dose reduction (approximately 10%) was also required for patients with moderate CKD. The dose reduction in the present study sample (24%) was greater than in both prior reports, possibly attributable to increased discrimination provided by patient matching or study sample differences or both. For example, our patients were almost exclusively of African ancestry, a population typically associated with higher warfarin dose requirement than patients of European ancestry. In contrast, slightly more than one-half of the patients in 1 of these prior studies were of African ancestry; however, they were not evenly distributed among the groups.

Discussion

We found that patients with moderate kidney disease required lower weekly warfarin doses to maintain therapeutic INR than matched patients with an eCrCl greater than 60 mL per min. In addition, patients with kidney disease spent significantly less time in therapeutic range. In turn, this decrease in anticoagulation stability resulted in an increase in the clinic management required to maintain therapeutic anticoagulation, as reflected in the proportion of clinic visits with dose manipulations and decreased time between scheduled visits.

Kidney Disease and Warfarin Dose

Our finding that CKD was associated with lower warfarin dose requirements is consistent with previous suggestions and clinical data. Based upon evaluation of data from pharmacokinetic studies, Dreisbach and Lertora (2008) concluded that chronic kidney failure had significant effects on nonrenal drug clearance, protein binding, and drug volume distribution. Therefore, they advised caution when dosing warfarin for patients with CKD. Nonetheless, they emphasized that estimating the magnitude of the dose effects would be difficult without empirical data. The first data to confirm reduction in required warfarin dose for patients with CKD were obtained by Limdi et al. (2009). Their study compared warfarin dose, anticoagulation control, and hemorrhagic events in patients with mild or no CKD, patients with moderate CKD (estimated glomerular filtration rate [eGFR] of 30-59 mL per min per 1.73 m²), and those with severe disease (eGFR less than 30 mL per min per 1.73 m²). Patients with severe CKD required a lower dose (approximately 20% less than that of patients with no or mild disease), had fewer clinic visits with INR values within the target range, and were at increased bleeding risk. A follow-up study from the same group (Limdi et al., 2010) reported that dose reduction (approximately 10%) was also required for patients with moderate CKD. The dose reduction in the present study sample (24%) was greater than in both prior reports, possibly attributable to increased discrimination provided by patient matching or study sample differences or both. For example, our patients were almost exclusively of African ancestry, a population typically associated with higher warfarin dose requirement than patients of European ancestry. In contrast, slightly more than one-half of the patients in 1 of these prior studies were of African ancestry; however, they were not evenly distributed among the groups.

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management. The decrease in anticoagulation stability found in patients with CKD versus the comparison group was associated with an increase in the proportion of clinic visits with dose changes and in the frequency of any type of dose manipulation (Figure 3). In contrast, the proportion of transient dose adjustments did not significantly differ between groups. The latter manipulation usually occurs in response to diet changes (typically, for vitamin K-containing food) or a failure to take the prescribed dose. Such events reflect daily life, and as such, there is no compelling reason to suppose that these events would occur with different frequency in our 2 groups. In contrast, changes in prescribed weekly dose typically occur in response to unexplained INR fluctuations that dose adjustments have failed to correct. As such, they likely reflect a more fundamental problem. Therefore, we propose that the greater proportion of dose changes not only reflects an effect of kidney dysfunction, but also suggests that this effect itself fluctuates. Specifically, both increases and decreases in dose occurred throughout the observation period; that is, there was not simply a succession of dose decreases in response to decreases in kidney function.

The increase in dose changes and subsequent decreased time between visits for patients with CKD placed additional burden on the clinic. Specifically, the extra visits required for patients with CKD would amount to at least another 30 hours (4½ visits x 20 patients x 20 min scheduled per appointment) of annual clinic time in this sample of 20 patients. Thus, the decreased anticoagulation stability associated with CKD has practical implications and warrants further investigation.

Implications for Managed Care

Patients with CKD comprised more than 10% of our database and also a sizeable proportion of all patients on anticoagulation; in the Randomized Evaluation of Long Term Anticoagulation Therapy (RE-LY) trial, approximately 20% had eCrCl <50 mL per min (patients with eCrCl <30 mL per min were excluded). Therefore, CKD’s detrimental effect on anticoagulation stability has managed care implications. Specifically, widespread use of new anticoagulants depends upon their cost-effectiveness and efficacy versus warfarin. Shah and Gage (2011) concluded, based on Markov model analysis incorporating data from RE-LY and other trials, that dabigatran (150 mg) was cost-effective in patients with atrial fibrillation at high risk for hemorrhage or stroke unless INR control with warfarin was excellent (TTR >72.6%).4 Similarly, anticoagulation stability influences adverse event frequency. Wallentin et al. (2010) examined the effect of INR control in the RE-LY trial and found that the rate of cardiovascular events decreased as TTR increased for warfarin-treated patients.5 Furthermore, event rates for all cardiovascular endpoints, including mortality, were lower with warfarin at high TTR (>72.6%) than with dabigatran.5 Hence, excellent anticoagulation control not only provides better outcomes, but also reduces costs. Therefore, stratification of outcome and cost analysis on the basis of renal function is warranted.

But, how can anticoagulation control be enhanced in warfarin-treated patients to meet the target for excellence? One method would be to increase the number of patients enrolled in specialist anticoagulation clinics, which typically attain higher TTR levels than community-based practice—21—the comparison group’s average TTR in the present study was 74%. Additional improvement may be achieved by addressing factors known to affect anticoagulation control. Nevertheless, recognition that CKD adversely affects anticoagulation stability is alone insufficient to provide benefit. The instability exhibited by patients with CKD, both in our study and in the earlier report of Limdi et al. (2009),3 suggests that current approaches to anticoagulation management (i.e., the same approach as for other patients) are inadequate for CKD patients and should be revised. However, further investigation is necessary to identify key instability characteristics and thereby develop a more effective management strategy.

Limitations

First, we did not assess any of the interpatient genetic differences known to influence warfarin dose. Currently identified genetic factors can produce significant dose variability between patients of European or Asian ancestry; however, their role in interpatient dose variability for patients of African ancestry is not yet established.16 In addition, genotype has not been associated with anticoagulation stability in this population.17 Thus, because all but 2 of our patients were of African ancestry, it appears unlikely that the lower average dose or decrease in anticoagulation stability we observed in patients with CKD is attributable to genetic differences.

Second, although we found reduced warfarin dose and decreased anticoagulation stability, we did not identify a mechanism for the changes. One hypothesis for reduced dose requirement is a change in warfarin binding. However, in a small subsample of patients for whom serum albumin data was available, we found no between-group difference (mean [SD] for comparison group [n=7] 4.0 [0.4] grams per deciliter [g per dL] vs. CKD [n=12] 4.0 [0.2] g per dL, P=0.843). Dreisbach and Lertora proposed other ways that reduced kidney function could affect drug metabolism and transport;7 for example, increased circulating uremic factors, increased cytokines, and decreased cytochrome P450 metabolism.18 We did not investigate these possibilities. However, in another study, we found that warfarin-treated patients who experienced an episode of in-hospital acute kidney injury (AKI) exhibited INR-dependent responses. When the initial INR was subtherapeutic, AKI slowed INR increase with subsequent warfarin doses versus that found in patients without AKI. Conversely, when initial INR was supratherapeutic, AKI slowed
It is therefore possible that the decreased anticoagulation stability and increased frequency of dose manipulation found in the current study reflected episodes of AKI superimposed on CKD. However, the myriad factors that influence warfarin dose will likely confound efforts to determine the mechanism in patient studies; thus, assessment in animal models may provide greater insight.

Third, our sample size of 40 patients could be considered too small. Studies usually attempt to compensate for large variability in warfarin response by enrolling large numbers of patients; for example, Limdi et al. (2009) included 578 patients in their study of kidney function and warfarin response. Nevertheless, it is also typical for the results of such studies to require subsequent adjustment; Limdi et al. (2009) adjusted for genetic factors and for clinical factors including age, race, gender, body mass index, vitamin K intake, alcohol, smoking, interacting drugs, and comorbid conditions. However, in some cases, the precise method of adjustment is not stated. Our approach to minimize interpatient variability was to match patients based on several factors previously demonstrated to produce large variation in warfarin response. We believe that this approach provides more robust results than would be the case for a study of 40 randomly selected warfarin-treated patients.

Fourth, there are several factors for which we did not directly control that could have affected the results; for example, differences in pharmacist practice, poor or erratic adherence to treatment, and additional dietary interactions with warfarin. However, we do not believe that these factors affected the outcomes for the following reasons. All patients in both groups were seen by multiple pharmacists during the study; therefore, differences in pharmacists’ individual practice would not confound our results. Questions regarding adherence to warfarin are part of each clinic visit and no subjects were noted to have poor adherence beyond an occasional missed or extra dose. Sometimes potential dietary interactions (e.g., consumption of cranberry juice) were noted; however, such interactions will be transient. Cases of dose errors and transient dietary interactions would, depending upon the INR measurement, either result in no dose manipulation or in a dose adjustment; we found no difference in dose adjustments between the groups.

Finally, the findings of the present study are based on analysis of a predominantly female and African ancestry population. Nevertheless, similar reduced anticoagulation stability was reported in a cohort that was 40% male and 60% European ancestry; therefore, we believe that our patient management results are representative of patients with CKD in general.

**Conclusions**

We found that patients with moderate CKD required lower warfarin doses to maintain therapeutic anticoagulation than patients with an eCrCl greater than 60 mL per min. Furthermore, moderate kidney disease was associated with significant decreases in anticoagulation stability and concomitant increases in the amount of required clinic management. Finally, we propose that the natural history of warfarin response in patients with CKD should be further examined. With such knowledge, even if the mechanism responsible remains unknown, it may be possible to devise strategies to manage the response to warfarin therapy more efficiently and thereby enhance anticoagulation stability.

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**DISCLOSURES**

There was no external or specific funding for this research. The authors reported no financial or other potential conflicts of interest. Concept and design were performed by Whittaker with the assistance of Clemente and Garwood. Data were collected primarily by Kleinow and Whittaker and interpreted primarily by Whittaker with the assistance of Kleinow. The manuscript was written by Whittaker and Kleinow and revised by Whittaker with the assistance of Garwood.

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