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Potential impact of Substituting estimated Glomerular Filtration Rate for estimated Creatinine Clearance for dosing of Direct Oral Anticoagulants

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Abbreviated title: DOAC dosing and estimated of renal clearance

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ABSTRACT

Background /Objectives: Direct oral anticoagulant (DOAC) doses in stroke prevention trials for non-valvular atrial fibrillation and FDA-approved prescribing recommendations are based on renal clearance estimated by Cockcroft and Gault method (CrCL-CG). Most laboratories report estimated glomerular filtration rate (GFR). The objective was to determine the potential impact of substituting GFR estimates for CrCL-CG for DOAC dosing.

Design: Simulation and retrospective data analysis

Setting: Community, academic institution, nursing home

Participants: 4687 non-institutionalized civilians (aged 19-80 y) from NHANES (2011-2) and 208 medically stable research participants (aged 25-105 y).

Measurements: age, height, weight, sex, race, serum creatinine, CrCL-CG and GFR (by Modification of Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations). Outcome measures were dosing errors if GFR were substituted for CrCL-CG.

Results: Renal clearance estimates by all methods were highly correlated ($p<.0001$). However, at lower clearances substitution of GFR estimates for CrCL-CG resulted in failure to recognize needs for dose reductions of rivaroxaban or edoxaban in 28% of NHANES subjects and 47-56% of research subjects. At CrCL-CG below 30 ml/min, GFR estimates missed indicated dosage reductions for dabigatran in 18-21% of NHANES subjects and 57-86% of research subjects. Age and weight contributed to differences between renal clearance estimates ($p<.001$) but body-surface area correction of GFR did not reduce dosing errors. At CrCL-CG over 95 ml/min edoxaban is not recommended and GFResimates mis-classified 24% of NHANES and 39% of

research subjects. Correction for body-surface area reduced mis-classification to 7% (NHANES) and 14% (research subjects).

Conclusion: Substitution of glomerular filtration estimates for estimated creatinine clearance can lead to failure to recognize indications for reduced DOAC doses and potentially higher bleeding rates than in randomized trials.

Key words: direct oral anticoagulant, non-vitamin K oral anticoagulant, renal clearance, estimated glomerular filtration rate, creatinine clearance.

INTRODUCTION

Non-vitamin K antagonist direct oral anticoagulants (DOACs) have recently been introduced into clinical use for prevention of stroke in patients with non-valvular atrial fibrillation and treatment of patients with deep vein thrombosis or pulmonary emboli. (1-7) The DOACs are renally excreted and dosing recommendations for prevention of stroke in patients with non-valvular atrial fibrillation are based on renal clearance estimated by the Cockcroft and Gault equation (8) (dabigatran, rivaroxaban, and edoxaban), age (apixaban), weight (apixaban, edoxaban), and creatinine (apixaban, edoxaban), concomitant administration of strong P-glycoprotein inhibitors or inducers (dabigatran, rivaroxaban, apixaban, edoxaban), and presence of cirrhosis (by Child-Pugh class(9)). Currently, most clinical laboratories report estimated glomerular filtration rate (GFR) and not estimated creatinine clearance. Estimation equations for creatinine clearance and GFR differ in values assigned to age, sex, weight, and race and were derived from different clinical populations. (8, 10-12) The majority of patients with atrial fibrillation are elderly and creatinine clearance estimates predict a steeper decline with advancing age than GFR estimates. This raises the possibility that substitution of commonly reported GFR for estimated creatinine clearance could result in selection of a dose that differs from recommended dosing guidelines. The purpose of this study was to compare estimates of creatinine clearance and GFR and determine the extent to which calculated doses would differ if GFR were used in place of estimated creatinine clearance.

METHODS

Overall Design. Simulation using NHANES 2011-2012 data and a research database to calculate GFR and creatinine clearance followed by analysis of differences in dosing recommendations if GFR were substituted for creatinine clearance.

Participants. Data came from two databases: 1) the 2011-2012 National Health and Nutrition Examination Survey (NHANES) of civilian non-institutionalized adults from ages 18-80 years without medical exclusions (http://www.cdc.gov/nchs/nhanes.htm) and 2) a consecutive sample of medically stable adults enrolled in research studies approved by the UCSF Human Research Committee during 2012-2014 that included very elderly and nursing home residents with exclusion of people receiving dialysis, with active malignancies, or hypercalcemia. (13-16)

Measurements. Age, sex, race, height, weight, and serum creatinine data were analyzed. Estimated creatinine clearance (CrCL-CG) was calculated using the Cockcroft and Gault formula(8): where CrCL-CG = 140-Age(y) * Weight (kg)/ 72* Creatinine (mg/dL; 1.0 mg/dL=88.4 μmol/L). Estimated glomerular filtration rate (GFR) was calculated using the simplified MDRD equation(10): GFR (mL/min/1.73 M^2) = $175 \times (Scr)^{-1.154} \times (Age)^{-0.203} \times (0.742$ if female) × (1.212 if African American) and the 2-level race CKD-EPI formula (11) : GFR=141 × $\min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if black] where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

Statistical Design and Data Analysis. Data are presented as mean ±S.D. Differences between the two sample groups were tested by unpaired t test. Relationships between CrCL-CG and GFR and between GFR estimates were examined by linear regression and Lin's concordance correlation

coefficient. The relationship between differences in CrCL-CG and GFR estimates in relation to age and weight were graphically examined and then tested by multiple regression for independent effects and ANOVA for interactions.

Definition of Recommended Doses. Dosage information from FDA-approved package inserts was defined as the recommended dose. Adjustments for creatinine clearance when prescribed for stroke prevention in non-valvular atrial fibrillation are: dabigatran reduce dose for CrCL-CG of 15-30 ml/min (to 75 mg twice daily vs. 150 mg twice daily), rivaroxaban reduce dose for CrCL-CG of 15 to 49 ml/min (to 15 mg once daily vs 20 mg), edoxaban reduce dose for CrCl of 30 to 49 ml/min (to 30 mg daily from 60 mg once daily) with edoxaban not recommended for CrCL-CG >95 ml/min. Apixaban was not included in analyses as recommended dose reductions are not based on estimated renal clearance but on the presence of at least two of the following criteria: age 80y or older, weight 60 kg or less, and serum creatinine of 1.5mg/dL or greater, and co-medications.

Differences in Doses calculated by GFR as compared to CrCL-CG. Raw numbers and percents of subjects with differences between estimates of GFR and CrCL-CG that would have resulted in a dosing difference are presented.

RESULTS

Subject Data. Demographic and laboratory results are presented in Table 1. NHANES civilian non-institutionalized adults had a younger mean age and slightly higher proportion of blacks than the research subjects while mean weight and serum creatinine were similar. Independent of method, mean estimates of renal clearance were lower in the research subject sample compared

to the NHANES sample (Table 1). Estimates of creatinine clearance and glomerular filtration by all methods were highly correlated ($p<.0001$) with stronger correlations between glomerular filtration estimates than between estimates of creatinine clearance and glomerular filtration. Although not routinely performed, correction of glomerular filtration estimates for body surface area improved correlations with creatinine clearance estimates. (see Appendix Table 1 for between method correlations). Table 2 compares estimates of CrCL to GFR estimates at CrCL cutpoints at which dosing adjustments are recommended. Plots comparing individual estimates of renal clearance by the differing methods are presented in Fig 1.

In the NHANES sample 28 per cent of subjects with creatinine clearances below 50 ml/min would not be correctly classified using any of the GFR equations (even after body surface area correction) and 47-56 per cent of research subjects samples would not be correctly classified. For CrCL-CG between 30 and 50 ml/min, the mean overestimate in the NHANE sample using the CKD-EPI equation was 4.9 with a S.D. of 13.3 and 5 ± 13.4 for the MDRD equation. For research subjects, the overestimation was greater with a mean of 14.5 ±12.8 using the CKD-EPI equation and 18.8 ±15.1 using the MDRD equation. Although fewer subjects in either sample had creatinine clearances below 30 ml/min, similar proportions of GFR overestimation were seen (18-21% of NHANES subjects and in 43-86% of research subjects depending on the method, see Table 2). Very few subjects had creatinine clearances below 15 ml/min for which dabigatran, edoxaban, and rivaroxaban are not recommended and GFR estimates correctly identified these individuals (1 in the research sample and 10 in NHANES).

A CrCL-CG over 95 ml/min identifies patients with non-valvular atrial fibrillation for whom edoxaban is not currently indicated. Table 2 and Figure 2 present comparisons of creatinine clearance and GFR estimates for subjects with creatinine clearances over 95 ml/min. Almost

two thirds of the NHANES sample had creatinine clearances over 95 ml/min and one quarter of these had GFR estimates (CKD-EPI) below 95 ml/min/1.73 M^2. A smaller proportion (36%) of research subjects had creatinine clearances over 95 ml/min, but the misclassification rate was higher with thirty-nine per cent having GFR estimates below 95 ml/min/1.73 M^2.

In both the NHANES and research samples, weight ($p<.0001$) and age ($p<.0001$) contributed to differences between creatinine clearance and GFR estimates with weight explaining more of the difference. Plots of differences of individual renal clearance estimates by age and weight are presented in Figure 3. Individuals with lower weights had higher estimated GFR compared to creatinine clearance and individuals with higher weights had lower GFR estimates than creatinine clearance estimates. Age effects were characterized by higher GFR compared to CrCL-CG in older adults and lower GFR compared to CrCL-CG in younger adults. In the NHANES sample there was greater racial diversity and a race effect was detected on the differences between estimates ($p<.0042$) with interactions detected between sex and weight ($p<.0001$), race and weight p($<.0001$), and sex, weight and age ($p=.0065$). In the smaller research sample, weaker interactions between sex and weight ($p<.03$) and sex*age*weight ($p<.03$) were detected with insufficent racial diversity for analyses.

Although overall correlation between estimates of creatinine clearance and GFR improved after correction for body surface area, correction for body surface area did not reduce misclassification of subjects with creatinine clearance rates below 30 or below 50 ml/min for whom DOAC dose reductions would be recommended. (Table 2). In contrast to results at lower creatinine clearances, correction of GFR estimates for body surface area greatly reduced misclassifications of subjects with creatinine clearance over 95 ml/min (i.e., who would be ineligible for edoxaban).

DISCUSSION

The potential advantages of DOACs compared to warfarin include a short time for onset of effect and time to reach steady-state, lack of requirement for laboratory monitoring of anticoagulation effect, and simplified dosing with fewer recognized drug or nutrition interactions and without known genetic variation in responses. Despite simplified dosing considerations compared to warfarin, there is not one dose of any DOAC for all patients. Recommended dosage adjustments for the prevention of stroke in patients with non-valvular atrial fibrillation are based on slightly different parameters for each DOAC but include renal function, co-administration of strong P-glycoprotein inhibitors and significant hepatic disease for dabigatran, rivaroxaban and edoxaban; and, age, weight, and creatinine and concomitant potent P-glycoprotein/CYP3A inhibitors for apixaban and rivaroxaban.

The importance of adjusting doses based on renal function was established with the first DOAC, dabigatran, when higher rates of bleeding were encountered that were in part due to lack of adjustment of doses for reduced renal function. (17) FDA-approved package labeling provides information to guide dose adjustments based on creatinine clearance in ml/min estimated with the Cockcroft and Gault equation that incorporates age, weight (measured and not ideal), serum creatinine and a sex factor as this was the method used in all the large randomized clinical trials to establish efficacy and safety. (18-21). The Cockcroft and Gault equation was developed from a limited population sample with non-standardized creatinine measurements. Subsequent research has led to the development of a series of formulae by the Modification of Diet in Renal Disease Study and Chronic Kidney Disease Epidemiology Collaboration that more closely estimate glomerular filtration rates at higher rates and define renal disease status. (10-12) Clinical laboratories now use standardized creatinine measurements and routinely report GFR with either

the MDRD or the CKD-EPI equations that incorporate age, sex, serum creatinine, and race, and do not include weight. Results are reported as ml/min/1.73 M^2. Laboratories do not currently report creatinine clearance as estimated by Cockcroft and Gault equation or body surface area-corrected estimates of GFR.

The National Kidney Disease Education Program (NKDEP) states that differences in GFR based on the MDRD Study and the Cockcroft-Gault equations will not lead to a difference in drug dosages for the majority of patients and that either equation can be used.(22) These conclusions were largely based on a simulation study of pooled data from about 5500 research study participants and clinical populations with directly measured GFR that compared MDRD and Cockcroft and Gault estimates both uncorrected and corrected for BSA. (23) The participants had a mean age of 47 ± 15 years and although elderly patients were underrepresented, the greatest discordance between estimates was seen in those over 65 years of age. The study pre-dated the publication of the CKD-EPI equations that the National Kidney Foundation recommends for use in people over age 70 years. (22) A comparison of results of renal clearance estimation that included glomerular filtration rate by CKD-EPI and MDRD equations as well as the Cockcroft and Gault estimated creatinine clearance and measured 24-hour creatinine clearance has been performed in a sample of men and women over the age of 70 years. (24) The results showed both CKD-EPI and MDRD consistently produced higher estimates than either measured creatinine clearance or Cockcroft and Gault estimates. (24)

The DOACs were developed after standardization of creatinine assays with IDMS-traceable creatinine values and dosing and patient exclusion during clinical trials based on renal function were determined with the Cockcroft and Gault equation with standardized creatinine

measurements. (18-21) The mean and median age of participants in randomized trials to establish the efficacy and safety of dabigatran, rivaroxaban and apixaban was 70-73 years with most over age 65 years. (18-20) Thus, in contrast to the lack of data on the elderly in many cardiovascular trials, the efficacy and safety of these medications as well as dosing guidelines using current standardized creatinine measurements and/or estimated creatinine clearance by the Cockcroft and Gault formula are known.

The present work examined data from adults in the large NHANES sample of civilian non-institutionalized U.S. residents and a group of research subjects including community-dwelling and nursing home residents who were medically stable but included very elderly and frail. In agreement with NKDEP conclusions, in the NHANES sample of young and middle-aged adults with fewer elderly and very elderly, the majority had estimated creatinine clearances that were not in the range of recommended DOAC dosage adjustments and CrCL-CG and GFR estimates were more likely to be concordant. The research subject sample had a mean estimated creatinine clearance that was lower and a greater proportion demonstrated differences between CrCL-CG and GFR (CKD-EPI). Differences were characterized by higher estimates of GFR than creatinine clearance at older ages and in people at lower weights and lower estimates of GFR than creatinine clearance in people with higher weights. However, rather than population differences or examining accuracy of the algorithms, the focus of this work was on determining the potential effects that differences in estimates of creatinine clearance and GFR would have on recognition of a need for dose reduction or choice of a DOAC for stroke prevention in an individual with non-valvular atrial fibrillation.

For rivaroxaban and edoxaban, dose reductions are recommended for patients with creatinine clearance below 50 ml/min and for dabigatran reduced doses are recommended at a creatinine clearance below 30 ml/min. The data show that if GFR (as MDRD or CKD-EPI) were substituted for creatinine clearance estimates, from one fifth to one half of people that should receive a reduced dose of a DOAC would not be identified.

The National Kidney Disease Education Program (NKDEP) concludes that for most drugs, adjusting for BSA is not necessary for determining drug dosing. However, if using GFR in very large or very small patients, the reported GFR should be multiplied by the body surface area to obtain GFR in units of ml/min. (http://nkdep.nih.gov/resources/ckd-drug-dosing-508.pdf). Despite improved correlations between GFR and CrCL-CG after correction of CKD-EPI estimates for body surface area, there was little to no improvement in concordance of estimates for creatinine clearances below 50 ml/min or below 30 ml/min for which DOAC dose reductions are recommended. While the DOACs have not been classified as narrow therapeutic window medications, higher concentrations are associated with greater inhibition of clotting. The clinical consequence of a failure to reduce DOAC doses might be a higher rate of bleeding than in clinical trials, or potentially avoidable bleeding complications. While bleeding rates were not examined in this study, an increased risk of bleeding has been demonstrated for other anticoagulants when patients receive an excess dose in relation to estimated renal clearance. (25) Bleeding risks are also consistently highest in older patients, small patients and female patients. As these are also the same patients for whom estimates of glomerular filtration are higher than estimates of creatinine clearance by Cockcroft and Gault formula, use of the Cockcroft and Gault creatinine clearance measure is advocated for dosage adjustments to reduce excess dosing. (24, 25) Advocating for use of the Cockcroft and Gault creatinine clearance measure should not be

limited to only DOACs or anticoagulants, however, as most FDA-approved drug labeling recommendations for dosage reductions based on renal function are based on creatinine clearance using the Cockcroft and Gault equation.

The work also has implications for people with higher estimated creatinine clearances. The recommendation not to approve the use of edoxaban in patients with creatinine clearance over 95 ml/min was based on less benefit on stroke prevention in patients with non-valvular atrial fibrillation in patients with creatinine clearance over 95 ml/min. (21) In the NHANES and research subjects analyzed in this study, one third to one half of subjects with creatinine clearance estimated to be over 95 ml/min had GFR estimates below 95 ml/min/1.73 M^2. Misclassifying patients as eligible for edoxaban based on a GFR estimate lower than the creatinine clearance of 95 ml/min could result in the choice of a less efficacious therapy. In contrast to the results at lower ranges of creatinine clearance, correction of the CKD-EPI equation for body surface area greatly reduced the number of people that would be misclassified as eligible for edoxaban based on GFR (to 7% in the NHANES sample and 14% in the research sample).

Study limitations. The purpose was not to determine the equation that most accurately predicts glomerular filtration rate and glomerular filtration rate was not directly measured. The prevalence of use of GFR vs creatinine clearance calculations was not determined but the most commonly routinely reported GFR equations were evaluated. The work reflects the potential impact of substituting clinical laboratory data as currently presented to health care professionals treating patients.

In conclusion, substitution of GFR for estimated creatinine clearance can lead to a failure to recognize patients with non-valvular atrial fibrillation for whom reduced doses of DOACs are recommended as well as failure to recognize patients that should not receive edoxaban. The failure to recognize the indication for a DOAC dosage reduction could result in a greater risk of bleeding than seen in the DOAC randomized studies of efficacy and safety. For evaluation for edoxaban therapy for prevention of stroke in patients with atrial fibrillation, GFR corrected for BSA may improve patient selection. In the absence of DOAC concentration or pharmacologic effect data to guide dosing or data from clinical trials or FDA recommendations based on GFR, DOAC dosing adjustments based on renal function should be guided by estimates of creatinine clearance and not GFR.

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Conflict of Interest: Dr. Schwartz has consulted for Bristol-Myers Squibb, Inc.

Author contributions: Janice B. Schwartz, MD was responsible for conception and design of the study, acquisition, analysis, and interpretation of data, drafting and revision of the manuscript and had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Janice Schwartz: study conception, design, data collection, data analysis, manuscript preparation.

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Elements of Financial/Personal Conflicts	***Author 1** **J. Schwartz**	
	Yes	**No**
Employment or Affiliation		x
Grants/Funds		x
Honoraria		x
Speaker Forum		x
Consultant	x	
Stocks		x

Royalties		x
Expert Testimony		x
Board Member		x
Patents		x
Personal Relationship		x

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GRAPHICS

Table 1. Demographic and Laboratory Results for Subject Data Analyzed

	NHANES Sample	Research Sample
Number of subjects	4687	208
Sex (men, women)	2339, 2348	102, 106
Race (black, white)	1244, 3443	33, 175
Age (y)	46 ±17	68 ±19*
Range	19-80	25-105
n>age 65	949	111
n>age 80	0	73
Weight (kg)	81 ±21	79.4 ± 20.5
Range	35-216	45.4-175.2
Body Surface Area (M^2)	1.90±.25	1.86 ±0.25
Range	1.29-2.62	1.22-3.03
Creatinine (mg/dL)	0.9 ±0.4	1.00 ±0.58
Range	0.41-8.18	0.3-9.5
CrCL-CG (ml/min)	118 ±46	83 ±40*
Range	14-235	7-450
GFR , MDRD (ml/min/1.73 M^2)	99±27	77±26*
Range	7-284	7-159
GFR, CKD-EPI (ml/min/1.73 M^2)	98 ±23	76±25*
Range	6-177	7-130
GFR, CKD-EPI (ml/min) ^	107±28	82± 30*
Range	7-226	8-172

Data are mean ± S.D. unless otherwise noted. y=year. To convert creatinine to SI units: 1.0 mg/dL=88.4 μmol/L. e=estimated, CrCL denotes creatinine clearance by Cockcroft and Gault

formula, GFR=glomerular filtration rate, MDRD = Modification of Diet in Renal Disease (MDRD) Study equation modified in 2005, CKD-EPI is the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (11), * denotes significant between group differences ($p<.00001$ uncorrected for multiple comparisons). ^Corrected for Body Surface Area.

Table 2. Comparisons of Glomerular Filtration Rate and Creatinine Clearance Estimates for Creatinine Clearance Ranges with Recommended DOAC Dosing Adjustments.

	NHANES Sample (n=4687)					Research Sample (n=208)				
	CrCL<50 ml/min (n=127)		CrCL <30 ml/min (n=34)		CrCL>95 ml/min (n-3171)	CrCL<50 ml/min (n=45)		CrCL < 30 ml/min (n=7)		CrCL >95 ml/min (n=74)
	GFR <50 n, %	GFR ≥50 (discordant)	GFR <30	GFR ≥30 (discordant)	GFR <95 (discordant)	GFR <50	GFR ≥50 (discordant)	GFR <30	GFR ≥30 (discordant)	GFR <95 (discordant)
MDRD (ml/min/1.73 $M^{2)}$ *(Per Cent)*	91 (72)	**36 (*28)***	27 (*7*)	**7 (*2*)**	**1355 (*43*)**	20 (*44*)	**25 (*56*)**	1 (*14*)	**6 (*86*)**	**37 (*50*)**
CKD-EPI(ml/min/1.73 $M^{2)}$	93 (*73*)	**34 (*27*)**	28 (*82*)	**6 (*18*)**	**756 (*24*)**	22 (*49*)	**23 (*51*)**	3 (*43*)	**4 (*57*)**	**29 (*39*)**
CKD-EPI ^ (ml/min)	92 (*72*)	**35 (*28*)**	28 (*8*)	**6 (*18*)**	**220 (*7*)**	24 (*53*)	**21(*47*)**	4 (*57*)	**3 (*43*)**	**10 (*14*)**

CrCL denotes creatinine clearance using the Cockcroft and Gault formula, e=estimated, GFR=glomerular filtration rate, MDRD = Modification of Diet in Renal Disease **(**MDRD**)** Study equation modified in 2005, CKD-EPI is the Chronic Kidney Disease

372Epidemiology Collaboration (CKD-EPI) formula (11). ^Corrected for Body Surface Area. Grey shading and boldface indicate
373discordant results that could result in dosing errors or errors in choice of a DOAC.

374

Figure Legends

Figure 1. Title: Comparisons of estimated creatinine clearance and glomerular filtration rates and potential impact on DOAC dosing.

Legend: Creatinine clearance estimated by the Cockcroft Gault method is plotted on the horizontal axis and Glomerular Filtration Rate estimated using the CKD-EPI method is plotted on the vertical axis. In the left panel are individual data for NHANES subjects (x) and the right panel presents individual data for research subjects (diamonds). Shaded vertical bars indicate creatinine clearance ranges for which dose reductions of direct oral anticoagulants (DOACs) are recommended (between 30-49 ml/min and/or below 30 ml/min). The darker shaded area of the vertical bars indicates GFR estimates that are higher than creatinine clearance and would result in higher than recommended doses (or dosing errors) if GFR were substituted for creatinine clearance. The light shaded area of the bars indicates concordant estimates that would result in the same DOAC dose for the individual. See Table 2 for absolute numbers and percentages of those correctly and incorrectly classified.

Figure 2. Title: Comparison of estimated creatinine clearance and glomerular filtration rates at higher creatinine clearance rates.

Creatinine clearance estimated by the Cockcroft Gault method is plotted on the horizontal axis and Glomerular Filtration Rate estimated using the CKD-EPI method is plotted on the vertical axis for individuals with creatinine clearance rates over 80 ml/min. In the left panel are individual data for NHANES subjects (x) and the right panel presents individual data for research subjects (diamonds). Use of the DOAC doxaban is not indicated for patients with a creatinine clearance over 95 ml/min. The darker shading indicates errors in considering

eligibility for edoxaban if GFR were substituted for creatinine clearance either due to inappropriate selection of edoxaban for a patient because GFR is below 95 ml/min/1.73 M^2 when creatinine clearance is over 95 ml/min, or when edoxaban is not considered for use because GFR is over 95 ml/min/1.73 M^2 when creatinine clearance is below 95 ml/min. The lighter shading indicates concordance or agreement for appropriateness of a patient for edoxaban administration if GFR estimates were substituted for creatinine clearance estimates. See Table 2 for absolute numbers and percentages of those correctly and incorrectly classified.

Figure 3. Title: Differences between estimated creatinine clearances and body surface area corrected estimated glomerular filtration rates.

Legend: Differences between estimates of creatinine clearance estimated by Cockcroft and Gault method and GFR estimated by the CKD-EPI method corrected for body surface area are plotted on the vertical axis with subject weight and age on the horizontal axis. Solid black symbols present data on weight and open or grey symbols present age data. NHANES data are on the left and the research subject sample data on the right. Positive values reflect higher GFR-CKD-EPI estimates compared to creatinine clearance estimated by the Cockcroft and Gault method and negative values reflect lower GFR-CKD-EPI estimates compared to CrCL-CG. The dotted line denotes zero difference between estimates. Note the scales are different in the two panels.

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Fig 1

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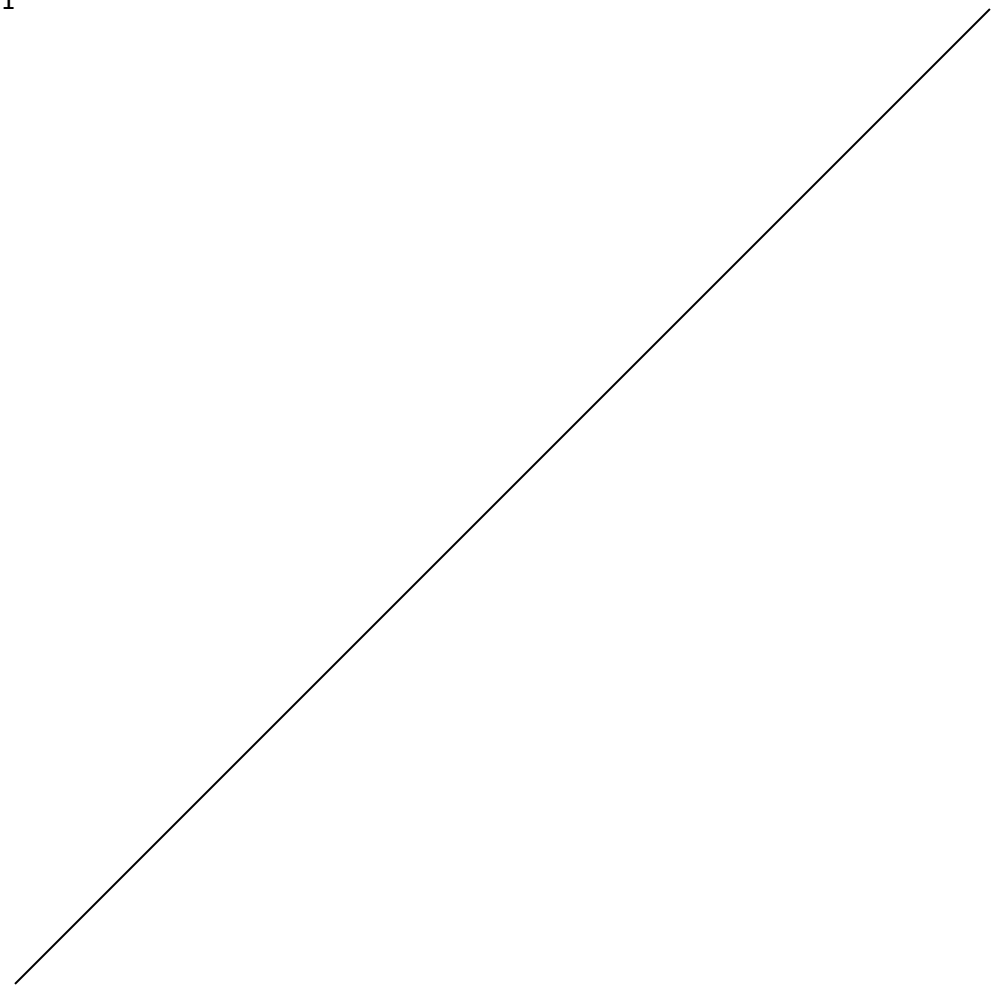

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Fig 3.

Appendix

Table 1. Comparisons of Renal Clearance Estimates

	Regression Correlation Coefficient	Lin's Concordance Correlation Coefficient	95% confidence Interval
Research Sample			
Creatinine Clearance*			
vs. GFR- MDRD^	r^2=0.503	0.497	0.392-0.589
vs. GFR-CKD-EPI	$r^{2=}$0.628	0.697	0.639-0.748
vs. GFR-CKD-EPI –BSA cor°	r^2 = 0.866	0.898	0.875-0.918
GFR- MDRD vs. CKD-EPI	r^2= 0.885	0.659	0.579-0.726
NHANES sample			
Creatinine Clearance			
vs. GFR- MDRD	r^2 =0.445	0.463	0.447-0.478
vs. GFR-CKD-EPI	r^2 =0.475	0.482	0.467-0.496
vs. GFR-CKD-EPI –BSA cor	r^2 =0.806	0.773	0.764 to 0.780
GFR-MDRD vs. CKD-EPI	r^2= 0.848	0.899	0.894 to 0.904

*Creatinine clearance (ml/min) estimated by Cockcroft and Gault formula, ^GFR= glomerular filtration rate (ml/min/1.73 M^2), MDRD= estimated by Modification of Diet in Renal Disease (MDRD) Study equation modified in 2005, CKD-EPI=estimated the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (11). °BSAcor=corrected for body surface area in units ml/min

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