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

3

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8

9 Abbreviated title: DOAC dosing and estimated of renal clearance

10

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15

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17ABSTRACT

18**Background /Objectives:** Direct oral anticoagulant (DOAC) doses in stroke prevention trials
19for non-valvular atrial fibrillation and FDA-approved prescribing recommendations are based on
20renal clearance estimated by Cockcroft and Gault method (CrCL-CG). Most laboratories report
21estimated glomerular filtration rate (GFR). The objective was to determine the potential impact
22of substituting GFR estimates for CrCL-CG for DOAC dosing.

23**Design:** Simulation and retrospective data analysis

24**Setting:** Community, academic institution, nursing home

25**Participants:** 4687 non-institutionalized civilians (aged 19-80 y) from NHANES (2011-2) and
26208 medically stable research participants (aged 25-105 y).

27**Measurements:** age, height, weight, sex, race, serum creatinine, CrCL-CG and GFR (by
28Modification of Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology
29Collaboration (CKD-EPI) equations). Outcome measures were dosing errors if GFR were
30substituted for CrCL-CG.

31**Results:** Renal clearance estimates by all methods were highly correlated ($p < .0001$). However,
32at lower clearances substitution of GFR estimates for CrCL-CG resulted in failure to recognize
33needs for dose reductions of rivaroxaban or edoxaban in 28% of NHANES subjects and 47-56%
34of research subjects. At CrCL-CG below 30 ml/min, GFR estimates missed indicated dosage
35reductions for dabigatran in 18-21% of NHANES subjects and 57-86% of research subjects. Age
36and weight contributed to differences between renal clearance estimates ($p < .001$) but body-
37surface area correction of GFR did not reduce dosing errors. At CrCL-CG over 95 ml/min
38edoxaban is not recommended and GFR estimates mis-classified 24% of NHANES and 39% of

39research subjects. Correction for body-surface area reduced mis-classification to 7% (NHANES)
40and 14% (research subjects).

41**Conclusion:** Substitution of glomerular filtration estimates for estimated creatinine clearance
42can lead to failure to recognize indications for reduced DOAC doses and potentially higher
43bleeding rates than in randomized trials.

44

45**Key words:** direct oral anticoagulant, non-vitamin K oral anticoagulant, renal clearance,
46estimated glomerular filtration rate, creatinine clearance.

47INTRODUCTION

48Non-vitamin K antagonist direct oral anticoagulants (DOACs) have recently been introduced
49into clinical use for prevention of stroke in patients with non-valvular atrial fibrillation and
50treatment of patients with deep vein thrombosis or pulmonary emboli. (1-7) The DOACs are
51renally excreted and dosing recommendations for prevention of stroke in patients with non-
52valvular atrial fibrillation are based on renal clearance estimated by the Cockcroft and Gault
53equation (8) (dabigatran, rivaroxaban, and edoxaban), age (apixaban), weight (apixaban,
54edoxaban), and creatinine (apixaban, edoxaban), concomitant administration of strong P-
55glycoprotein inhibitors or inducers (dabigatran, rivaroxaban, apixaban, edoxaban), and presence
56of cirrhosis (by Child-Pugh class(9)). Currently, most clinical laboratories report estimated
57glomerular filtration rate (GFR) and not estimated creatinine clearance. Estimation equations for
58creatinine clearance and GFR differ in values assigned to age, sex, weight, and race and were
59derived from different clinical populations. (8, 10-12) The majority of patients with atrial
60fibrillation are elderly and creatinine clearance estimates predict a steeper decline with advancing
61age than GFR estimates. This raises the possibility that substitution of commonly reported GFR
62for estimated creatinine clearance could result in selection of a dose that differs from
63recommended dosing guidelines. The purpose of this study was to compare estimates of
64creatinine clearance and GFR and determine the extent to which calculated doses would differ if
65GFR were used in place of estimated creatinine clearance.

66METHODS

67Overall Design. Simulation using NHANES 2011-2012 data and a research database to calculate
68GFR and creatinine clearance followed by analysis of differences in dosing recommendations if
69GFR were substituted for creatinine clearance.

70Participants. Data came from two databases: 1) the 2011-2012 National Health and Nutrition
71Examination Survey (NHANES) of civilian non-institutionalized adults from ages 18-80 years
72without medical exclusions (<http://www.cdc.gov/nchs/nhanes.htm>) and 2) a consecutive sample
73of medically stable adults enrolled in research studies approved by the UCSF Human Research
74Committee during 2012-2014 that included very elderly and nursing home residents with
75exclusion of people receiving dialysis, with active malignancies, or hypercalcemia. (13-16)

76 Measurements. Age, sex, race, height, weight, and serum creatinine data were analyzed.
77Estimated creatinine clearance (CrCL-CG) was calculated using the Cockcroft and Gault
78formula(8): where $CrCL-CG = 140 - Age(y) * Weight(kg) / 72 * Creatinine(mg/dL; 1.0$
79 $mg/dL = 88.4 \mu mol/L)$. Estimated glomerular filtration rate (GFR) was calculated using the
80simplified MDRD equation(10): $GFR(mL/min/1.73 M^2) = 175 \times (Scr)^{-1.154} \times (Age)^{-0.203} \times (0.742$
81if female) $\times (1.212$ if African American) and the 2-level race CKD-EPI formula (11) : $GFR = 141$
82 $\times \min(Scr/\kappa, 1)^\alpha \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times 1.159$ [if black] where Scr is
83serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for
84males, min indicates the minimum of Scr/ κ or 1, and max indicates the maximum of Scr/ κ or 1.

85Statistical Design and Data Analysis. Data are presented as mean $\pm$ S.D. Differences between the
86two sample groups were tested by unpaired t test. Relationships between CrCL-CG and GFR and
87between GFR estimates were examined by linear regression and Lin's concordance correlation

88coefficient. The relationship between differences in CrCL-CG and GFR estimates in relation to
89age and weight were graphically examined and then tested by multiple regression for
90independent effects and ANOVA for interactions.

91*Definition of Recommended Doses.* Dosage information from FDA-approved package inserts
92was defined as the recommended dose. Adjustments for creatinine clearance when prescribed for
93stroke prevention in non-valvular atrial fibrillation are: dabigatran reduce dose for CrCL-CG of
9415-30 ml/min (to 75 mg twice daily vs. 150 mg twice daily), rivaroxaban reduce dose for CrCL-
95CG of 15 to 49 ml/min (to 15 mg once daily vs 20 mg), edoxaban reduce dose for CrCl of 30 to
9649 ml/min (to 30 mg daily from 60 mg once daily) with edoxaban not recommended for CrCL-
97CG >95 ml/min. Apixaban was not included in analyses as recommended dose reductions are
98not based on estimated renal clearance but on the presence of at least two of the following
99criteria: age 80y or older, weight 60 kg or less, and serum creatinine of 1.5mg/dL or greater, and
100co-medications.

101*Differences in Doses calculated by GFR as compared to CrCL-CG.* Raw numbers and percents
102of subjects with differences between estimates of GFR and CrCL-CG that would have resulted in
103a dosing difference are presented.

104

105**RESULTS**

106Subject Data. Demographic and laboratory results are presented in Table 1. NHANES civilian
107non-institutionalized adults had a younger mean age and slightly higher proportion of blacks
108than the research subjects while mean weight and serum creatinine were similar. Independent of
109method, mean estimates of renal clearance were lower in the research subject sample compared

110to the NHANES sample (Table 1). Estimates of creatinine clearance and glomerular filtration by
111all methods were highly correlated ($p<.0001$) with stronger correlations between glomerular
112filtration estimates than between estimates of creatinine clearance and glomerular filtration.
113Although not routinely performed, correction of glomerular filtration estimates for body surface
114area improved correlations with creatinine clearance estimates. (see Appendix Table 1 for
115between method correlations). Table 2 compares estimates of CrCL to GFR estimates at CrCL
116cutpoints at which dosing adjustments are recommended. Plots comparing individual estimates
117of renal clearance by the differing methods are presented in Fig 1.

118In the NHANES sample 28 per cent of subjects with creatinine clearances below 50 ml/min
119would not be correctly classified using any of the GFR equations (even after body surface area
120correction) and 47-56 per cent of research subjects samples would not be correctly classified. For
121CrCL-CG between 30 and 50 ml/min, the mean overestimate in the NHANE sample using the CKD-EPI
122equation was 4.9 with a S.D. of 13.3 and 5 ± 13.4 for the MDRD equation. For research subjects, the
123overestimation was greater with a mean of 14.5 ± 12.8 using the CKD-EPI equation and 18.8 ± 15.1 using
124the MDRD equation. Although fewer subjects in either sample had creatinine clearances below
12530 ml/min, similar proportions of GFR overestimation were seen (18-21% of NHANES
126subjects and in 43-86% of research subjects depending on the method, see Table 2). Very few
127subjects had creatinine clearances below 15 ml/min for which dabigatran, edoxaban, and
128rivaroxaban are not recommended and GFR estimates correctly identified these individuals (1 in
129the research sample and 10 in NHANES).

130A CrCL-CG over 95 ml/min identifies patients with non-valvular atrial fibrillation for whom
131edoxaban is not currently indicated. Table 2 and Figure 2 present comparisons of creatinine
132clearance and GFR estimates for subjects with creatinine clearances over 95 ml/min. Almost

133two thirds of the NHANES sample had creatinine clearances over 95 ml/min and one quarter of
134these had GFR estimates (CKD-EPI) below 95 ml/min/1.73 M². A smaller proportion (36%) of
135research subjects had creatinine clearances over 95 ml/min, but the misclassification rate was
136higher with thirty-nine per cent having GFR estimates below 95 ml/min/1.73 M².

137In both the NHANES and research samples, weight (p<.0001) and age (p<.0001) contributed to
138differences between creatinine clearance and GFR estimates with weight explaining more of the
139difference. Plots of differences of individual renal clearance estimates by age and weight are
140presented in Figure 3. Individuals with lower weights had higher estimated GFR compared to
141creatinine clearance and individuals with higher weights had lower GFR estimates than
142creatinine clearance estimates. Age effects were characterized by higher GFR compared to
143CrCL-CG in older adults and lower GFR compared to CrCL-CG in younger adults. In the
144NHANES sample there was greater racial diversity and a race effect was detected on the
145differences between estimates (p<.0042) with interactions detected between sex and weight
146(p<.0001), race and weight p(<.0001), and sex, weight and age (p=.0065). In the smaller research
147sample, weaker interactions between sex and weight (p<.03) and sex*age*weight (p<.03) were
148detected with insufficient racial diversity for analyses.

149Although overall correlation between estimates of creatinine clearance and GFR improved after
150correction for body surface area, correction for body surface area did not reduce
151misclassification of subjects with creatinine clearance rates below 30 or below 50 ml/min for
152whom DOAC dose reductions would be recommended. (Table 2). In contrast to results at lower
153creatinine clearances, correction of GFR estimates for body surface area greatly reduced
154misclassifications of subjects with creatinine clearance over 95 ml/min (i.e., who would be
155ineligible for edoxaban).

156DISCUSSION

157The potential advantages of DOACs compared to warfarin include a short time for onset of effect
158and time to reach steady-state, lack of requirement for laboratory monitoring of anticoagulation
159effect, and simplified dosing with fewer recognized drug or nutrition interactions and without
160known genetic variation in responses. Despite simplified dosing considerations compared to
161warfarin, there is not one dose of any DOAC for all patients. Recommended dosage adjustments
162for the prevention of stroke in patients with non-valvular atrial fibrillation are based on slightly
163different parameters for each DOAC but include renal function, co-administration of strong P-
164glycoprotein inhibitors and significant hepatic disease for dabigatran, rivaroxaban and edoxaban;
165and, age, weight, and creatinine and concomitant potent P-glycoprotein/CYP3A inhibitors for
166apixaban and rivaroxaban.

167 The importance of adjusting doses based on renal function was established with the first DOAC,
168dabigatran, when higher rates of bleeding were encountered that were in part due to lack of
169adjustment of doses for reduced renal function. (17) FDA-approved package labeling provides
170information to guide dose adjustments based on creatinine clearance in ml/min estimated with
171the Cockcroft and Gault equation that incorporates age, weight (measured and not ideal), serum
172creatinine and a sex factor as this was the method used in all the large randomized clinical trials
173to establish efficacy and safety. (18-21). The Cockcroft and Gault equation was developed from a
174limited population sample with non-standardized creatinine measurements. Subsequent research
175has led to the development of a series of formulae by the Modification of Diet in Renal Disease
176Study and Chronic Kidney Disease Epidemiology Collaboration that more closely estimate
177glomerular filtration rates at higher rates and define renal disease status. (10-12) Clinical
178laboratories now use standardized creatinine measurements and routinely report GFR with either

179the MDRD or the CKD-EPI equations that incorporate age, sex, serum creatinine, and race, and
180do not include weight. Results are reported as ml/min/1.73 M². Laboratories do not currently
181report creatinine clearance as estimated by Cockcroft and Gault equation or body surface area-
182corrected estimates of GFR.

183The National Kidney Disease Education Program (NKDEP) states that differences in GFR based
184on the MDRD Study and the Cockcroft-Gault equations will not lead to a difference in drug
185dosages for the majority of patients and that either equation can be used.(22) These conclusions
186were largely based on a simulation study of pooled data from about 5500 research study
187participants and clinical populations with directly measured GFR that compared MDRD and
188Cockcroft and Gault estimates both uncorrected and corrected for BSA. (23) The participants had
189a mean age of 47 ± 15 years and although elderly patients were underrepresented, the greatest
190discordance between estimates was seen in those over 65 years of age. The study pre-dated the
191publication of the CKD-EPI equations that the National Kidney Foundation recommends for use
192in people over age 70 years. (22) A comparison of results of renal clearance estimation that
193included glomerular filtration rate by CKD-EPI and MDRD equations as well as the Cockcroft
194and Gault estimated creatinine clearance and measured 24-hour creatinine clearance has been
195performed in a sample of men and women over the age of 70 years. (24) The results showed both
196CKD-EPI and MDRD consistently produced higher estimates than either measured creatinine
197clearance or Cockcroft and Gault estimates. (24)

198The DOACs were developed after standardization of creatinine assays with IDMS-traceable
199creatinine values and dosing and patient exclusion during clinical trials based on renal function
200were determined with the Cockcroft and Gault equation with standardized creatinine

201measurements. (18-21) The mean and median age of participants in randomized trials to
202establish the efficacy and safety of dabigatran, rivaroxaban and apixaban was 70-73 years with
203most over age 65 years. (18-20) Thus, in contrast to the lack of data on the elderly in many
204cardiovascular trials, the efficacy and safety of these medications as well as dosing guidelines
205using current standardized creatinine measurements and/or estimated creatinine clearance by the
206Cockcroft and Gault formula are known.

207The present work examined data from adults in the large NHANES sample of civilian non-
208institutionalized U.S. residents and a group of research subjects including community-dwelling
209and nursing home residents who were medically stable but included very elderly and frail. In
210agreement with NKDEP conclusions, in the NHANES sample of young and middle-aged adults
211with fewer elderly and very elderly, the majority had estimated creatinine clearances that were
212not in the range of recommended DOAC dosage adjustments and CrCL-CG and GFR estimates
213were more likely to be concordant. The research subject sample had a mean estimated creatinine
214clearance that was lower and a greater proportion demonstrated differences between CrCL-CG
215and GFR (CKD-EPI). Differences were characterized by higher estimates of GFR than
216creatinine clearance at older ages and in people at lower weights and lower estimates of GFR
217than creatinine clearance in people with higher weights. However, rather than population
218differences or examining accuracy of the algorithms, the focus of this work was on determining
219the potential effects that differences in estimates of creatinine clearance and GFR would have
220on recognition of a need for dose reduction or choice of a DOAC for stroke prevention in an
221individual with non-valvular atrial fibrillation.

222For rivaroxaban and edoxaban, dose reductions are recommended for patients with creatinine
223clearance below 50 ml/min and for dabigatran reduced doses are recommended at a creatinine
224clearance below 30 ml/min. The data show that if GFR (as MDRD or CKD-EPI) were
225substituted for creatinine clearance estimates, from one fifth to one half of people that should
226receive a reduced dose of a DOAC would not be identified.

227The National Kidney Disease Education Program (NKDEP) concludes that for most drugs,
228adjusting for BSA is not necessary for determining drug dosing. However, if using GFR in very
229large or very small patients, the reported GFR should be multiplied by the body surface area to
230obtain GFR in units of ml/min. (<http://nkdep.nih.gov/resources/ckd-drug-dosing-508.pdf>).

231Despite improved correlations between GFR and CrCL-CG after correction of CKD-EPI
232estimates for body surface area, there was little to no improvement in concordance of estimates
233for creatinine clearances below 50 ml/min or below 30 ml/min for which DOAC dose reductions
234are recommended. While the DOACs have not been classified as narrow therapeutic window
235medications, higher concentrations are associated with greater inhibition of clotting. The clinical
236consequence of a failure to reduce DOAC doses might be a higher rate of bleeding than in
237clinical trials, or potentially avoidable bleeding complications. While bleeding rates were not
238examined in this study, an increased risk of bleeding has been demonstrated for other
239anticoagulants when patients receive an excess dose in relation to estimated renal clearance. (25)
240Bleeding risks are also consistently highest in older patients, small patients and female patients.
241As these are also the same patients for whom estimates of glomerular filtration are higher than
242estimates of creatinine clearance by Cockcroft and Gault formula, use of the Cockcroft and Gault
243creatinine clearance measure is advocated for dosage adjustments to reduce excess dosing. (24,
24425) Advocating for use of the Cockcroft and Gault creatinine clearance measure should not be

245limited to only DOACs or anticoagulants, however, as most FDA-approved drug labeling
246recommendations for dosage reductions based on renal function are based on creatinine
247clearance using the Cockcroft and Gault equation.

248The work also has implications for people with higher estimated creatinine clearances. The
249recommendation not to approve the use of edoxaban in patients with creatinine clearance over 95
250ml/min was based on less benefit on stroke prevention in patients with non-valvular atrial
251fibrillation in patients with creatinine clearance over 95 ml/min. (21) In the NHANES and
252research subjects analyzed in this study, one third to one half of subjects with creatinine
253clearance estimated to be over 95 ml/min had GFR estimates below 95 ml/min/1.73 M².
254Misclassifying patients as eligible for edoxaban based on a GFR estimate lower than the
255creatinine clearance of 95 ml/min could result in the choice of a less efficacious therapy. In
256contrast to the results at lower ranges of creatinine clearance, correction of the CKD-EPI
257equation for body surface area greatly reduced the number of people that would be misclassified
258as eligible for edoxaban based on GFR (to 7% in the NHANES sample and 14% in the research
259sample).

260Study limitations. The purpose was not to determine the equation that most accurately predicts
261glomerular filtration rate and glomerular filtration rate was not directly measured. The
262prevalence of use of GFR vs creatinine clearance calculations was not determined but the most
263commonly routinely reported GFR equations were evaluated. The work reflects the potential
264impact of substituting clinical laboratory data as currently presented to health care professionals
265treating patients.

266In conclusion, substitution of GFR for estimated creatinine clearance can lead to a failure to
267recognize patients with non-valvular atrial fibrillation for whom reduced doses of DOACs are
268recommended as well as failure to recognize patients that should not receive edoxaban. The
269failure to recognize the indication for a DOAC dosage reduction could result in a greater risk of
270bleeding than seen in the DOAC randomized studies of efficacy and safety. For evaluation for
271edoxaban therapy for prevention of stroke in patients with atrial fibrillation, GFR corrected for
272BSA may improve patient selection. In the absence of DOAC concentration or pharmacologic
273effect data to guide dosing or data from clinical trials or FDA recommendations based on GFR,
274DOAC dosing adjustments based on renal function should be guided by estimates of creatinine
275clearance and not GFR.

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280

281 Author contributions: Janice B. Schwartz, MD was responsible for conception and design of
282the study, acquisition, analysis, and interpretation of data, drafting and revision of the
283manuscript and had full access to all the data in the study and takes responsibility for the
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286

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Elements of Financial/Personal Conflicts	*Author 1 J. Schwartz	
	Yes	No
Employment or Affiliation		x
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Speaker Forum		x
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Royalties		x
Expert Testimony		x
Board Member		x
Patents		x
Personal Relationship		x

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354 filtration rate formula for classification of chronic kidney disease in patients with non-ST-
355 segment elevation acute coronary syndromes. *J Am Coll Cardiol*. 2008 51:991-6.

357Table 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

358

359Data are mean ± S.D. unless otherwise noted. y=year. To convert creatinine to SI units: 1.0

360mg/dL=88.4 μmol/L. e=estimated, CrCL denotes creatinine clearance by Cockcroft and Gault

361formula, GFR=glomerular filtration rate, MDRD = Modification of Diet in Renal Disease
362(MDRD) Study equation modified in 2005, CKD-EPI is the Chronic Kidney Disease
363Epidemiology Collaboration (CKD-EPI) formula (11), * denotes significant between group
364differences ($p < .00001$ uncorrected for multiple comparisons). ^Corrected for Body Surface Area.

365

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

368

	NHANES Sample (n=4687)					Research Sample (n=208)				
	CrCL<50		CrCL <30		CrCL>95	CrCL<50		CrCL < 30		CrCL >95
	ml/min		ml/min		ml/min	ml/min		ml/min		ml/min
	(n=127)		(n=34)		(n=3171)	(n=45)		(n=7)		(n=74)
	GFR	GFR	GFR	GFR	GFR	GFR	GFR	GFR	GFR	GFR
	<50	≥50	<30	≥30	<95	<50	≥50	<30	≥30	<95
	n, %	(discordant)		(discordant)	(discordant)		(discordant)		(discordant)	(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)

369

370CrCL denotes creatinine clearance using the Cockcroft and Gault formula, e=estimated, GFR=glomerular filtration rate, MDRD =
 371Modification 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

375 **Figure Legends**

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

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

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

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

397eligibility for edoxaban if GFR were substituted for creatinine clearance either due to
398inappropriate selection of edoxaban for a patient because GFR is below 95 ml/min/1.73 M²
399when creatinine clearance is over 95 ml/min, or when edoxaban is not considered for use because
400GFR is over 95 ml/min/1.73 M² when creatinine clearance is below 95 ml/min. The lighter
401shading indicates concordance or agreement for appropriateness of a patient for edoxaban
402administration if GFR estimates were substituted for creatinine clearance estimates. See Table 2
403for absolute numbers and percentages of those correctly and incorrectly classified.

404**Figure 3.** Title: Differences between estimated creatinine clearances and body surface area
405corrected estimated glomerular filtration rates.

406Legend: Differences between estimates of creatinine clearance estimated by Cockcroft and
407Gault method and GFR estimated by the CKD-EPI method corrected for body surface area are
408plotted on the vertical axis with subject weight and age on the horizontal axis. Solid black
409symbols present data on weight and open or grey symbols present age data. NHANES data are
410on the left and the research subject sample data on the right. Positive values reflect higher GFR-
411CKD-EPI estimates compared to creatinine clearance estimated by the Cockcroft and Gault
412method and negative values reflect lower GFR-CKD-EPI estimates compared to CrCL-CG. The
413dotted line denotes zero difference between estimates. Note the scales are different in the two
414panels.

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Fig 1

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427Fig 3.

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434

435Appendix

436Table 1. Comparisons of Renal Clearance Estimates

437

	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 ^o	$r^2 = 0.866$	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	$r^2=0.806$	0.773	0.764 to 0.780
cor			
GFR-MDRD vs. CKD-EPI	$r^2= 0.848$	0.899	0.894 to 0.904

438

439*Creatinine clearance (ml/min) estimated by Cockcroft and Gault formula, [^]GFR= glomerular
 440filtration rate (ml/min/1.73 M²), MDRD= estimated by Modification of Diet in Renal Disease
 441(MDRD) Study equation modified in 2005, CKD-EPI=estimated the Chronic Kidney Disease
 442Epidemiology Collaboration (CKD-EPI) formula (11). ^oBSAcor=corrected for body surface area
 443in units ml/min

444

445

446X

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448