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Dabigatran Reversal With Idarucizumab in Patients With Renal Impairment

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ABSTRACT

BACKGROUND Dabigatran and idarucizumab, its reversal agent, are renally cleared.

OBJECTIVES The purpose of this study was to determine the extent of reversal and outcomes according to baseline renal function in dabigatran-treated nondialysis patients receiving idarucizumab.

METHODS In 503 patients in RE-VERSE AD (Reversal of Effects of Idarucizumab in Patients on Active Dabigatran), the extent of dabigatran reversal and clinical outcomes were compared according to baseline renal function (creatinine clearance: normal ≥80, mild 50 to <80, moderate 30 to <50, and severe <30 ml/min).

RESULTS Compared with patients with normal renal function, those with impaired renal function were older, were more often women, and had lower body mass indexes, more comorbidities, higher $CHADS_2$ scores, and higher dabigatran plasma levels despite more frequent use of lower-dose dabigatran regimens. Regardless of renal function, median reversal measured by dilute thrombin time was 100% within 4 h of idarucizumab administration, and over 98% of patients achieved this with corresponding undetectable levels of unbound dabigatran. By 12 or 24 h, 56% of patients with severe, 29.1% with moderate, and 9.2% with mild renal impairment had dabigatran levels >20 ng/ml compared with 8.3% of patients with normal renal function at baseline. Time to cessation of bleeding and the proportion with normal hemostasis with procedures were similar regardless of renal function, but patients with severe renal impairment had higher 30- and 90-day mortality rates.

CONCLUSIONS Idarucizumab completely reverses dabigatran in >98% of patients regardless of renal function. Although re-elevation of dabigatran levels within 12 to 24 h is more common with renal impairment, the time to bleeding cessation and the extent of hemostasis during procedures are similar. (Reversal of Dabigatran Anticoagulant Effect With Idarucizumab; NCT02104947) (J Am Coll Cardiol 2019;74:1760–8) © 2019 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Dabigatran etexilate (dabigatran) is an oral direct thrombin inhibitor that is licensed for the prevention of stroke in patients with atrial fibrillation, and for the prevention and treatment of venous thromboembolism (1). Idarucizumab is a humanized monoclonal antibody fragment that binds dabigatran with high affinity (2,3). The RE-VERSE AD (Reversal of Effects of Idarucizumab in Patients on Active Dabigatran) study demonstrated that idarucizumab rapidly and

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completely reverses the anticoagulant effect of dabigatran in patients presenting with uncontrolled or life-threatening bleeding and in those requiring urgent surgery or an invasive procedure (4,5).

Both dabigatran and idarucizumab are cleared by the kidneys, and many patients presenting with severe bleeding or requiring emergency interventions have acute or chronic renal impairment. The impact of renal impairment on the extent of dabigatran reversal by idarucizumab and on clinical outcomes has not been published. The objective of this analysis was to compare clinical characteristics, dabigatran levels, extent of reversal of dabigatran by idarucizumab, and clinical outcomes according to baseline renal function in patients enrolled in RE-VERSE AD.

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METHODS

PATIENTS AND PROCEDURES. RE-VERSE AD was a prospective cohort study that enrolled 503 patients from 34 countries. The design has been previously published (6). The study enrolled 2 groups of adults 18 years or older who were taking dabigatran: group A included patients with overt, uncontrolled, or life-threatening bleeding, while group B included patients who required urgent surgery or invasive procedure that could not be delayed for at least 8 h, and for which normal hemostasis was required. Patients were eligible for inclusion irrespective of their baseline renal function. After providing written informed consent, patients received 5 g of intravenous idarucizumab, which was given as 2 50-ml bolus infusions, each containing 2.5 g of idarucizumab, none >15 min apart. This 5-g dose was calculated to reverse the total body load of dabigatran in 99% of patients based on observed dabigatran exposure in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial (7,8). We collected blood for laboratory testing before and during the first 4 h after idarucizumab administration and then at 12 and 24 h after administration of idarucizumab.

OUTCOMES. The primary outcome was the maximum percentage reversal of the anticoagulant effect of dabigatran within 4 h of administration of idarucizumab. This was determined using the diluted thrombin time (dTT) or ecarin clotting time (ECT) tests, chosen because of their excellent correlation with plasma dabigatran concentrations (9). In this paper, we only report the results with the dTT because this test is widely available, whereas the ECT is primarily a research tool. Results with the ECT were similar to those obtained with the dTT and do not change any of our conclusions. All patients with an elevated clotting test above the upper limit of normal at baseline were evaluated. For these analyses, we report "unbound" dabigatran drug levels as measured by high performance liquid chromatography-mass spectrometry. This assay involves an initial ultracentrifugation step that removes protein and does not measure dabigatran that is bound to plasma proteins or to idarucizumab. Approximately 30% of circulating dabigatran is bound to plasma proteins, and blood levels reported in this paper are therefore approximately 30% lower than those that would be obtained using commercially available assays or using the high-performance liquid chromatography-mass spectrometry methodology used in RE-LY (7).

Secondary outcomes included time to cessation of bleeding in patients who presented with overt bleeding, and the degree of hemostasis during procedures in those requiring urgent interventions. We defined hemostasis as normal, mildly abnormal (e.g., slight oozing), moderately abnormal (e.g., controllable bleeding), and severely abnormal (e.g., severe refractory hemorrhage). We also collected information on stroke, myocardial infarction, systemic embolism, deep vein thrombosis, pulmonary embolism and 30- and 90-day mortality, and report these outcomes in all patients exposed to idarucizumab in RE-VERSE AD.

CATEGORIZATION OF RENAL FUNCTION. Patients were categorized according to renal function at presentation based on their creatinine clearance (creatinine clearance: normal renal function: ≥80 ml/min; mild renal impairment: 50 to <80 ml/min; moderate renal impairment: 30 to <50 ml/min; and severe renal impairment: <30 ml/min) calculated using the Cockcroft Gault equation based on actual body weight: for men: CrCl = ([140 − age in years] × weight in kg at visit 1 × 1.23)/(baseline creatinine in μmol/l); for women: CrCl = (0.85 × [140 − age in years] × [weight at visit 1] × 1.23)/(baseline creatinine in μmol/l). For each category of baseline renal function, patient characteristics, sites of bleeding, types of procedures, dabigatran levels at presentation, percentage reversal, proportions of patients achieving complete reversal, and 30- and 90-day mortality rates were compared. We used "unbound" dabigatran levels of 20 ng/ml as a cut-off for re-elevation of dabigatran at 12 or 24 h. Commercially available dabigatran assays often have a lower cut-off limit of 30 ng/ml (9), which is equivalent to 20 ng/ml "unbound" dabigatran (excluding dabigatran bound to plasma proteins).

STATISTICAL ANALYSIS. Data were analyzed using descriptive statistics expressed as the mean ± SD or

ABBREVIATIONS AND ACRONYMS

dTT = diluted thrombin time
ECT = ecarin clotting time
ICH = intracranial hemorrhage
IQR = interquartile range

TABLE 1 Baseline Characteristics of Patients Categorized According to Renal Function*

	Renal Function					
	Normal ≥80 ml/min (n = 108)	Mild 50 to <80 ml/min (n = 163)	Moderate 30 to <50 ml/min (n = 127)	Severe <30 ml/min (n = 91)	Missing† (n = 14)	Total (n = 503)
Age, yrs	67.0 ± 11.0	77.0 ± 7.5	80.0 ± 7.7	81.0 ± 9.4	78.0 ± 17.0	77 ± 10
Male	71 (65.7)	91 (55.8)	65 (51.2)	41 (45.1)	6 (42.9)	274 (54.5)
BMI, kg/m^2	32.0 ± 8.0	27.0 ± 5.8	26.0 ± 5.1	26.0 ± 6.0	27.0 ± 8.0	28.0 ± 6.6
CrCl, ml/min	100.9 (88–121)	60.2 (54–67)	39.9 (35–45)	21.0 (15–26)	–	52.6 (35–75)
CV risk factors						
Hypertension	81 (75.0)	123 (75.5)	109 (85.8)	74 (81.3)	7 (50.0)	394 (78.3)
CHF	27 (25.0)	60 (36.8)	56 (44.1)	38 (41.8)	1 (7.1)	182 (36.2)
Diabetes	35 (32.4)	42 (25.8)	47 (37.0)	24 (26.4)	4 (28.6)	152 (30.2)
Medical history						
Ischemic stroke/TIA	24 (22.2)	37 (22.7)	44 (34.6)	28 (30.8)	3 (21.4)	136 (27.0)
Prior major bleeding	6 (5.6)	11 (6.7)	14 (11.0)	4 (4.4)	2 (14.3)	37 (7.4)
Active cancer	9 (8.3)	15 (9.2)	9 (7.1)	9 (9.9)	1 (7.1)	43 (8.5)
Hemoglobin level, g/l	127 (104–142)	123 (95–136)	106 (80–172)	96 (82–114)	110 (91–126)	112 (90–134)
$CHADS_2$ score	2.0 ± 1.3	2.5 ± 1.3	3.2 ± 1.2	2.9 ± 1.4	2.1 ± 1.4	2.6 ± 1.4
Indication for anticoagulation						
Atrial fibrillation	95 (88.0)	156 (95.7)	126 (99.2)	88 (96.7)	13 (92.9)	478 (95.0)
Other	13 (12.0)	7 (4.3)	1 (0.8)	3 (3.3)	1 (7.1)	25 (5.0)
Dabigatran dose						
150 mg BID	59 (54.6)	51 (31.3)	27 (21.3)	11 (12.1)	3 (21.4)	151 (30.0)
110 mg BID	40 (37.0)	103 (63.2)	84 (66.1)	76 (83.5)	8 (57.1)	311 (61.8)
75 mg BID	1 (0.9)	6 (3.7)	11 (8.7)	4 (4.4)	2 (14.3)	24 (4.8)
Other	6 (5.6)	2 (1.2)	5 (3.9)	0 (0.0)	1 (7.1)	14 (2.8)
Missing	2 (1.9)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)
Time since last dabigatran dose, h	14 (9–23)	15 (9–25)	16 (10–24)	19 (10–30)	13 (8–21)	16 (9–26)
Dabigatran level,‡ ng/ml	48 (22–93)	70 (36–118)	128 (75–241)	231 (151–590)	76 (39–96)	94 (43–196)

Values are mean ± SD, n (%), or median (interquartile range). *Missing data include: BMI (n = 28), creatinine clearance (n = 14), hemoglobin (n = 8), dabigatran dose (n = 2), and dabigatran level (n = 26). †14 patients could not be categorized according to renal function because their creatinine data were missing. ‡Unbound dabigatran levels.

BID = twice daily; BMI = body mass index; $CHADS_2$ = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack; CHF = congestive heart failure; CrCl = creatinine clearance; CV = cardiovascular; TIA = transient ischemic attack.

median (interquartile range). Frequencies (n) and percentages (%) were used for categorical variables. Analyses were performed using the statistical software SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

BASELINE CHARACTERISTICS. The baseline characteristics in patients with severe, moderate, or mild renal impairment and in those with normal renal function are shown in Table 1. Compared with the normal renal function group, patients with mild, moderate, or severe renal impairment at the time of their enrollment were older, were more likely to be female, had lower body mass index and higher mean $CHADS_2$ (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack) scores, had lower hemoglobin levels, and were more likely to have hypertension and congestive heart failure. In addition, they were more likely to be taking dabigatran 75 or 110 mg twice daily than 150 mg twice daily, had a longer time since the last dose of dabigatran, and had higher baseline dabigatran plasma levels.

INDICATIONS FOR REVERSAL. Table 2 provides the indications for dabigatran reversal in the groups according to baseline renal function. Compared with the group with normal renal function, group A patients with any renal impairment were more likely to have been enrolled because of gastrointestinal bleeding and less likely to be enrolled with intracranial hemorrhage (ICH). Bleeding severity was similar irrespective of baseline renal function. Group B patients with moderate renal impairment were more likely to require abdominal surgery, and those with severe renal impairment more frequently had catheter placement predominantly due to acute renal injury than those with normal renal function or mild renal impairment. Patients in either group A or B with mild, moderate, or severe renal impairment were

TABLE 2 Indication for Dabigatran Reversal According to Baseline Renal Function

	Renal Function					
Index Event	Normal ≥80 ml/min	Mild 50 to <80 ml/min	Moderate 30 to <50 ml/min	Severe <30 ml/min	Missing*	Total
Group A: site of bleeding†	58	95	86	53	9	301
Intracranial hemorrhage	32 (55.2)	36 (37.9)	24 (28.0)	3 (6.0)	3 (33.0)	98 (33.0)
Gastrointestinal bleeds	14 (24.1)	41 (43.2)	46 (54.0)	33 (62.0)	3 (33.0)	137 (46.0)
Group A: severity of bleeding (ISTH criteria)	58	95	86	53	9	301
Major and life-threatening	52 (89.7)	81 (85.3)	77 (89.5)	46 (86.8)	9 (100.0)	265 (88.0)
Minor	6 (10.3)	13 (13.7)	7 (8.1)	6 (11.3)	0 (0.0)	32 (10.6)
Not assessable	0 (0.0)	1 (1.1)	2 (2.3)	1 (1.9)	0 (0.0)	4 (1.3)
Group B: surgery/procedure‡	50	68	41	38	5	202
Abdominal procedures	9 (18.0)	13 (19.1)	19 (46.3)	8 (21.1)	0 (0.0)	49 (24.3)
Fractures	13 (26.0)	16 (23.5)	8 (19.5)	5 (13.2)	3 (60.0)	45 (22.3)
Vascular	14 (28.0)	15 (22.1)	3 (7.3)	2 (5.3)	0 (0.0)	34 (16.8)
Drainage	3 (6.0)	7 (10.3)	4 (9.8)	5 (13.2)	1 (20.2)	20 (9.9)
Catheter placement	2 (4.0)	10 (14.7)	3 (7.3)	14 (36.8)	0 (0.0)	29 (14.4)
Other	6 (12.0)	7 (10.3)	4 (9.8)	2 (5.3)	1 (20.0)	20 (9.9)
Groups A and B	108	163	127	91	14	503
Sepsis	1 (0.9)	6 (3.7)	14 (11.0)	13 (14.3)	0 (0.0)	34 (6.8)
Trauma-related	31 (28.7)	34 (20.9)	25 (19.7)	14 (15.4)	7 (50.0)	111 (22.1)

Values are n or n (%). Bleeding sites are only indicated for the 2 most frequent locations, other bleeds were also recorded but are not shown here. *Fourteen patients could not be categorized according to renal function because their creatinine data were missing. †Some patients had >1 site of bleeding; in 4 patients bleeding site was not identified. ‡Five patients did not undergo surgery or a procedure; surgery/procedure grouping was based on manual medical assessment.

more likely to have sepsis than those with normal renal function.

EXTENT OF DABIGATRAN REVERSAL. The extent of dabigatran reversal with idarucizumab according to baseline renal function is shown in Table 3 and in the Central Illustration. Median reversal based on the dTT was 100% in all groups. The proportion of patients achieving complete reversal within 4 h was similar irrespective of baseline renal function: 63 of 64 patients (98.4%) with normal renal function achieved complete reversal compared with 121 of 122 (99.2%) with mild, 112 of 113 (99.1%) with moderate, and 83 of 85 (97.6%) with severe renal impairment.

CLINICAL OUTCOMES. Clinical outcomes according to categories of renal function are displayed in Table 4. In group A non-ICH patients, the median time to cessation of bleeding was 2.2 h (IQR: 0.5 to 10.5 h) in those with normal renal function compared with 2.6 h (IQR: 1.8 to 7.2 h), 2.6 h (IQR: 1.5 to 5.8 h), and 3.3 h (IQR: 1.5 to 11.1 h) in those with mild, moderate, and severe renal impairment, respectively. In group B patients, normal hemostasis was achieved in 44 of 50 patients (93.6%) with normal renal function compared with 65 of 68 (95.6%), 37 of 41 (90.2%), and 34 of 38 (89.5%) of those with mild, moderate, and severe renal impairment, respectively. The median number of days in hospital was slightly longer in patients with renal impairment, and 30- and 90-day mortality were higher in those with severe renal function.

RE-ELEVATION OF DABIGATRAN LEVELS. Of the 503 patients enrolled, 113 (22.5%) had re-elevation of dabigatran levels to ≥20 ng/ml at either 12 or 24 h, including 9 of 108 patients (8.3%) with normal renal function and 15 of 163 (9.2%) with mild, 37 of 127 (29.1%) with moderate, and 51 of 91 patients (46.0%) with severe renal impairment. Renal function was not measured in 1 patient who had re-elevation of dabigatran levels. In patients with re-elevation at 12 or 24 h, mean levels were 7.4 ng/ml in those with normal renal function, and were 15.0, 46.7, and 124.0 ng/ml in patients with mild, moderate, and severe renal dysfunction, respectively.

Patients who had re-elevation of dabigatran levels above 20 ng/ml were more likely to be men (60.2% vs. 52.8%), have worse renal function (median CrCl 32.7 ml/min vs. 57.8 ml/min), and have a higher $CHADS_2$ score (mean 3.2 vs. 2.5); more often had hypertension, congestive heart failure, and diabetes; and were more likely to be septic. These patients more often had gastrointestinal bleeding (77.9% vs. 34.4%) and less often had ICH (9.1% vs. 40.6%). They also had higher baseline dabigatran levels (median 311 ng/ml vs. 71 ng/ml) than those without re-elevation of dabigatran levels at 12 or 24 h and

TABLE 3 Dabigatran Reversal Measured as dTT According to Categories of Baseline Renal Function

	Renal Function					
	Normal ≥80 ml/min	Mild 50 to <80 ml/min	Moderate 30 to <50 ml/min	Severe <30 ml/min	Missing*	Total
dTT						
Evaluable patients	64	122	113	85	12	396
Maximum reversal within 4 h	100 (100-100)	100 (100-100)	100 (100-100)	100 (100-100)	100 (100-100)	100 (100-100)
Proportion of patients achieving 100% reversal	63 (98.4)	121 (99.2)	112 (99.1)	83 (97.6)	12 (100.0)	391 (98.7)
Proportion of patients achieving 80% reversal	63 (98.4)	121 (99.2)	112 (99.1)	84 (98.8)	12 (100.0)	392 (99.0)
Dabigatran concentration†						
Evaluable patients	77	139	116	87	14	433
Patients achieving 100% reversal within 4 h	77 (100.0)	137 (98.6)	115 (99.1)	86 (98.9)	14 (100.0)	429 (99.1)
Patients restarted on dabigatran within 24 h	5 (6.5)	2 (1.4)	2 (1.7)	0 (0.0)	2 (14.3)	11 (2.5)
Dabigatran levels† at 12/24 h‡						
Dabigatran plasma levels at baseline	70 ± 85	106 ± 173	217 ± 320	447 ± 494	98 ± 87	190 ± 315
Individual maximum dabigatran plasma level at 12–24 h	7.4 ± 16	15.0 ± 106	46.7 ± 202	124 ± 225	7.7 ± 19	41.1 ± 159

Values are n, n (%), median (95% confidence interval), or mean ± SD. Reversal of unbound dabigatran concentration was defined as levels below 20 ng/ml. Reversal is shown for all patients with at least 1 post-dose value and with pre-dose dTT levels above the upper limit of normal (35.5 s). *Fourteen patients could not be categorized according to renal function because their creatinine data were missing. †Unbound dabigatran. ‡The maximum value from 12 or 24 h was taken for each patient.

dTT = diluted thrombin time.

13 (11.5%) had baseline dabigatran levels >1,000 ng/ml (Online Table 1).

Re-elevation of dabigatran levels to >20 ng/ml at 12 or 24 h was not associated with a longer time to hemostasis within 24 h, with a median time of 2.5 h versus 2.5 h in those who did not have re-elevation; however, a higher proportion of patients undergoing procedures had mildly or moderately abnormal hemostasis: 4 of 34 (11.8%) versus 9 of 163 (5.5%) (Online Table 2). Mortality at 30 days was also higher in those patients with re-elevations of dabigatran levels at 12 or 24 h (17.7% vs. 11.5%).

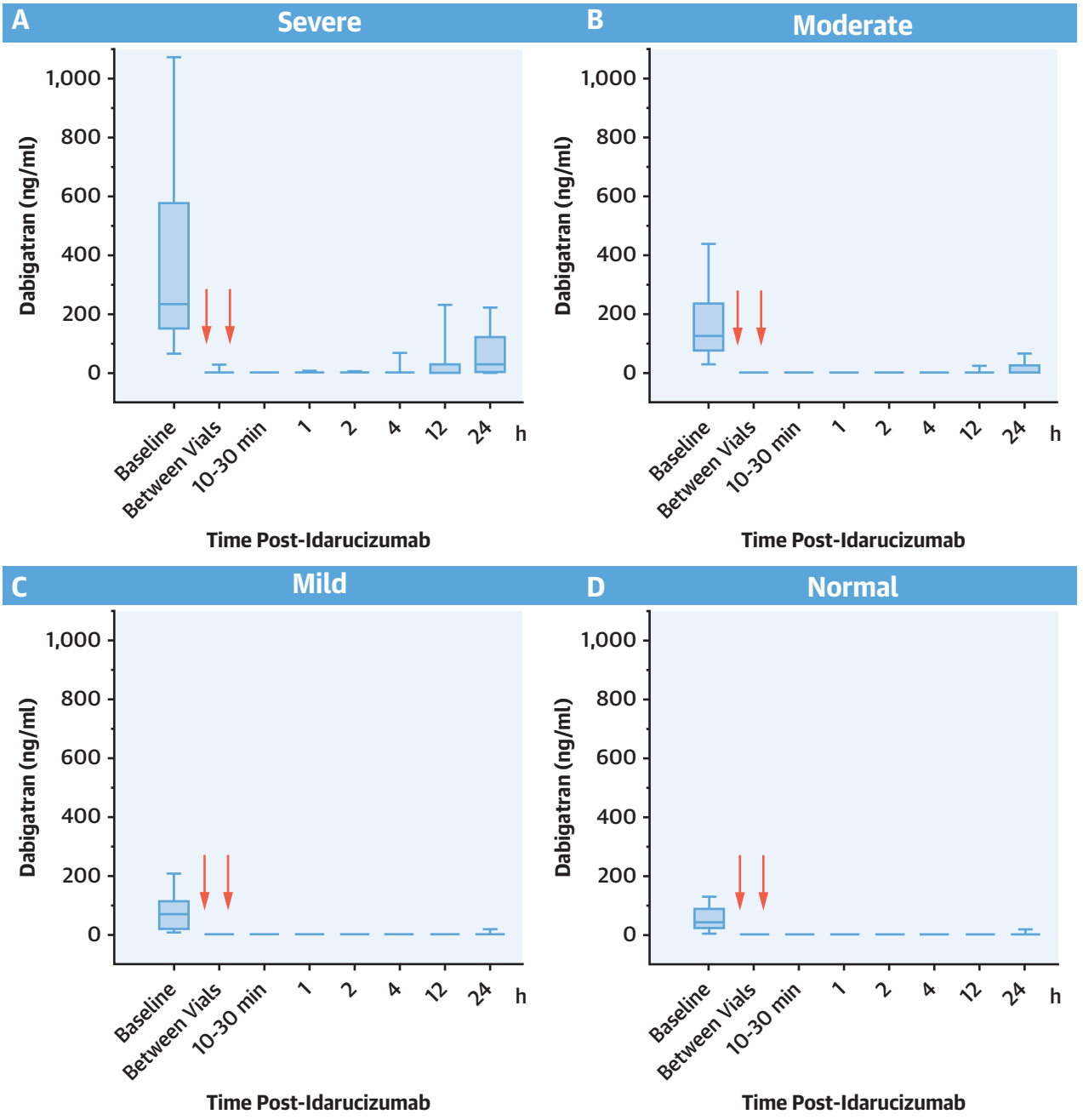
SECOND DOSE OF IDARUCIZUMAB. No patient with normal or mild renal impairment received a second dose of idarucizumab, whereas 3 patients who had moderate renal impairment and 5 patients who had severe renal impairment received a second dose. A total of 4 of these patients were enrolled in group A (3 GI bleeding, 1 hematuria), and 4 were enrolled in group B (2 required abdominal procedures due to ischemic bowel or perforation, and 2 required catheterization due to acute renal impairment). The second dose of idarucizumab was administered a median time of 51.4 h after the first dose, in 6 cases prompted by bleeding and in 2 cases because the patient required a further procedure (1 of these 2 also had bleeding). Information on dabigatran levels prior to administration of the second dose of idarucizumab, timing of the second dose, and outcome in these patients are shown in Online Table 3.

PATIENTS WITH BASELINE DABIGATRAN LEVELS >1,000 ng/ml. The mean age of the 15 patients with baseline levels >1,000 ng/ml (Online Table 4) was 79 years (range 62 to 93 years); 11 had severe, 3 had moderate, and 1 had mild renal impairment. A total of 9 patients were enrolled with gastrointestinal bleeding, 1 with hematuria, 4 for abdominal procedures, 1 for a diagnosis of suspected sepsis, and 1 with acute renal failure. Death occurred in 9 of these patients, a median of 2 days (range 1 to 15 days) post-idarucizumab. Of the 15 patients with baseline levels of unbound dabigatran >1,000 ng/ml, 12 were reversed within 4 h of administration of idarucizumab, whereas the 3 with the highest levels were only partially reversed. Of the 15, 13 had re-elevation of dabigatran levels above 20 ng/ml at 12 or 24 h; the other 2 patients did not have samples taken past 4 h and died within 24 h.

DISCUSSION

The results of these analyses reveal that regardless of baseline renal function or plasma dabigatran concentrations, a fixed dose of 5 g of idarucizumab provides complete and rapid reversal of the anticoagulant effects of dabigatran in patients presenting with serious bleeding or requiring urgent procedures. Although patients with impaired renal function were more likely to have re-elevation of dabigatran levels above 20 ng/ml at 12 or 24 h after idarucizumab administration, they had a similar time to bleeding cessation as patients without renal impairment, and normal hemostasis was achieved in almost all patients undergoing procedures regardless of baseline renal function. Thus, in the

CENTRAL ILLUSTRATION **Dabigatran Reversal Following Administration of Idarucizumab According to Baseline Renal Function**



Eikelboom, J.W. et al. J Am Coll Cardiol. 2019;74(14):1760–8.

Time course of dabigatran reversal following idarucizumab administration according to baseline renal function as estimate by the Cockcroft Gault formula: **(A)** severe renal dysfunction (estimated creatinine clearance [CrCl] <30 ml/min); **(B)** moderate renal dysfunction (CrCl 30 to <50 ml/min); **(C)** mild renal dysfunction (CrCl 50 to <80 ml/min); and **(D)** normal renal function (CrCl ≥80 ml/min). Data are presented as **box and whisker plots** in which the **top and the bottom of the rectangles** indicate the 75th and 25th percentiles, respectively. **The horizontal lines within the rectangles** indicate the 50th percentile, and the **lines above and below the rectangles** indicate the 90th and 10th percentiles, respectively. Median reversal within 4 h of idarucizumab administration as measured by the dilute thrombin time was 100% in all 4 groups. The **red arrows** represent administration of the 2 vials (2.5 g/vial) that make up the 5 g dose of idarucizumab.

TABLE 4 Clinical Outcomes According to Baseline Renal Function

Indication for Reversal	Renal Function					Total (n = 503)
	Normal ≥80 ml/min (n = 108)	Mild 50 to <80 ml/min (n = 163)	Moderate 30 to <50 ml/min (n = 127)	Severe <30 ml/min (n = 91)	Missing (n = 14)	
Group A: time to bleeding cessation	26	59	62	50	6	203
Evaluable patients	26	57	60	49	6	198
Bleeding cessation within 24 (+2) h	2.2 (0.5-10.5)	2.6 (1.8-7.2)	2.6 (1.5-5.8)	3.3 (1.5-11.1)	1.2 (1.0-3.0)	2.5 (1.4-7.2)
Group B: intraoperative hemostasis	47	68	41	36	5	197
Median time to surgery or procedure after first vial, h	1.5	1.7	1.4	1.5	2.9	1.6
Normal hemostasis	44 (93.6)	65 (95.6)	37 (90.2)	34 (94.4)	4 (80.0)	184 (93.4)
Mildly abnormal	3 (6.4)	3 (4.4)	3 (7.3)	1 (2.8)	0 (0.0)	10 (5.1)
Moderately abnormal	0 (0.0)	0 (0.0)	1 (2.4)	1 (2.8)	1 (20.0)	3 (1.5)
Severely abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any bleeding 24 h post-surgery/procedure	1 (2.1)	3 (4.4)	4 (9.8)	0 (0.0)	0 (0.0)	8 (4.1)
Overall						
Vital status at hospital discharge,* n (% alive)	96 (88.9)	149 (91.4)	113 (89.0)	70 (76.9)	10 (71.4)	438 (87.1)
Thrombotic events at 30 days†	3 (2.8)	7 (4.3)	7 (5.5)	5 (5.5)	1 (7.1)	23 (4.6)
Mortality at 30 days	12 (11.0)	14 (9.0)	13 (10.0)	22 (24.0)	4 (29.0)	65 (13.0)
Received second dose	0	0	3	5	0	8

Values are n, median (interquartile range), or n (%), unless otherwise indicated. *After first hospitalization. †If patients had >1 event, the first chronological date was used. One patient had a thrombotic event prior to idarucizumab and is excluded from the analysis.

majority of patients, a 5-g idarucizumab dose provided as complete and as effective dabigatran reversal in patients with renal impairment as in those with normal renal function.

Patients with impaired renal function at enrollment had higher mortality rates than those with normal renal function. These findings are consistent with their older age and greater comorbidity, and may also reflect delayed hospital presentation as suggested by longer time since the last dose of dabigatran. The fact that the extent of dabigatran reversal with idarucizumab was similar regardless of baseline renal function suggests that the higher mortality rates were unrelated to extent of reversal.

IDARUCIZUMAB DOSING. Dabigatran, idarucizumab, and the dabigatran-idarucizumab complex are cleared by the kidneys (10–12). Modeling studies performed prior to the start of the RE-VERSE AD study suggested that a 5-g dose of idarucizumab would be sufficient to fully bind the complete body load of dabigatran in almost all patients. Nonetheless, a substantial proportion of patients (~22%) had re-elevation of dabigatran levels exceeding 20 ng/ml at 12 or 24 h, particularly those with impaired renal function at baseline. The RE-LY trial excluded patients with severe renal impairment (8); thus, modeling studies based on the RE-LY population did not take into account extreme elevation of dabigatran levels in these types of patients. Potential explanations for re-elevation include delayed redistribution of the drug resulting in saturation of idarucizumab in patients with higher baseline levels of dabigatran, or progressive degradation of the dabigatran-idarucizumab complex in patients with impaired renal function, with corresponding release of dabigatran (13). If re-elevation is explained by dabigatran redistribution, giving a larger dose of the reversal agent might prevent re-elevation. However, if re-elevation is explained by degradation of the circulating dabigatran-idarucizumab complex, then additional idarucizumab would not be expected to prevent re-elevation.

DABIGATRAN DRUG LEVELS AND SITES OF BLEEDING. Despite the higher plasma dabigatran levels in patients with severe renal impairment, those who were enrolled in RE-VERSE AD more commonly presented with gastrointestinal bleeding than intracranial bleeding. This finding is in keeping with the results of the RE-LY trial, which demonstrated lower rates of intracranial hemorrhage with dabigatran than with warfarin regardless of baseline characteristics, including renal function (7). Although we cannot exclude an impact of selection bias, these observations suggest that the mechanism of action of the anticoagulant is a more important determinant of the risk of intracranial bleeding than the drug concentration.

CLINICAL CONSEQUENCES OF RE-ELEVATION OF DRUG LEVELS. As no association between renal impairment and either the time to cessation of bleeding or the achievement of normal hemostasis during procedures could be observed, it suggests that sustained reversal may not be essential for hemostasis. However, it is also possible that this observation reflects differences between the patients who presented with or without renal impairment. On the other hand, early recovery of anticoagulant activity may provide protection against thromboembolism, as suggested by the low rates of thrombotic complications observed in RE-VERSE AD. The overall rate of thrombotic events was 4.6% within 30 days after treatment, and 6.2% within 90 days. These rates of thrombosis after idarucizumab reversal of dabigatran appear to be similar or lower than those reported in clinical trials after reversal of vitamin K antagonists with prothrombin complex concentrates (14,15), and after reversal of rivaroxaban or apixaban with andexanet alfa (16–18).

STUDY LIMITATIONS. First, there was not an untreated control group (who did not receive idarucizumab) because this was deemed to be unethical. However, the analyses of the efficacy and safety of idarucizumab in patients with renal impairment remain informative, because patients with normal renal function served as a comparator. Second, renal function was recorded only once, at the time of enrollment; no post-idarucizumab measures of renal function were recorded. Third, we did not collect information on whether renal dysfunction was acute or chronic (or acute on chronic). When used in patients with acute kidney injury, equations to estimate creatinine clearance are difficult to interpret, and it is unclear what impact this may have had on our results. Fourth, we used an arbitrary cut-off of 20 ng/ml of unbound dabigatran to evaluate re-elevation of anticoagulant activity. However, this threshold was chosen because it corresponds to the lower limit of detection of the dabigatran using the commercially available dTT assay, and because it corresponds with levels at which almost all patients are reported to have normal hemostasis. Furthermore, it is likely that most invasive procedures can be safely performed with even somewhat higher dabigatran levels. Therefore, the 20 ng/ml cut-off is probably conservative.

IMPLICATIONS FOR CLINICAL PRACTICE. Our results have implications for clinical practice (19). Almost all patients treated with dabigatran who require reversal with idarucizumab can be expected to respond to therapy irrespective of baseline renal function. However, as many as one-half of patients with severe renal dysfunction will have some re-elevation of anticoagulant levels at 12 to 24 h compared with <10% of those with normal renal function at baseline. Although it is not necessary to await the results of coagulation testing or dabigatran drug levels prior to administering idarucizumab in patients with life-threatening emergencies, a baseline blood sample might be useful to identify those with extreme elevations of drug levels who may be at risk of re-elevation. Furthermore, if there is recurrent bleeding or a need for further surgery, repeat testing can help to identify rare cases of incomplete reversal or cases of re-elevation of drug levels who may benefit from a second dose of idarucizumab.

CONCLUSIONS

Regardless of baseline renal function, idarucizumab is effective for dabigatran reversal. Patients who present with severe renal impairment were more likely to demonstrate re-elevation of dabigatran anticoagulant activity, and overall had worse long-term clinical outcome, likely related to their index event, advanced age, and multiple comorbidities.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Idarucizumab completely reverses the anticoagulant effect of dabigatran in >98% of patients with life-threatening bleeding or facing urgent procedures, irrespective of renal function. Re-elevation of dabigatran blood levels within 12 to 24 h is more common in patients with renal impairment, but time to bleeding cessation and hemostasis during procedures are similar to those in patients with normal renal function.

TRANSLATIONAL OUTLOOK: Future studies should evaluate the safety and efficacy of idarucizumab as a specific reversal agent for dabigatran in patients with advanced kidney disease.

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APPENDIX For supplemental tables, please see the online version of this paper.