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Association of Intravenous Radiocontrast With Kidney Function
A Regression Discontinuity Analysis

Robert Goulden, MBBS; Brian H. Rowe, MD; Michal Abrahamowicz, PhD; Erin Strumpf, PhD; Robyn Tamblyn, PhD

+ Invited Commentary

+ Supplemental content

IMPORTANCE Radiocontrast has long been thought of as nephrotoxic; however, a number of recent observational studies found no evidence of an association between intravenous contrast and kidney injury. Because these studies are at high risk of confounding and selection bias, alternative study designs are required to enable more robust evaluation of this association.

OBJECTIVE To determine whether intravenous radiocontrast exposure is associated with clinically significant long-term kidney impairment, using a study design that permits stronger causal interpretation than existing observational research.

DESIGN, SETTING, AND PARTICIPANTS This cohort study included all emergency department patients aged 18 years or older undergoing D-dimer testing between 2013 and 2018 in the Canadian province of Alberta. A fuzzy regression discontinuity design was used, exploiting the fact that individuals just either side of the eligibility cutoff for computed tomographic pulmonary angiogram (CTPA)—typically 500 ng/mL—have markedly different probabilities of contrast exposure, but should otherwise be similar with respect to potential confounders.

EXPOSURES Intravenous contrast in the form of a CTPA.

MAIN OUTCOMES AND MEASURES Estimated glomerular filtration rate (eGFR) up to 6 months following the index emergency department visit.

RESULTS During the study period 156 028 individuals received a D-dimer test. The mean age was 53 years, 68 206 (44%) were men and 87 822 (56%) were women, and the mean baseline eGFR level was 86 mL/min/1.73 m^2. Patients just above and below the CTPA eligibility cutoff were similar in terms of measured confounders. There was no evidence for an association of contrast with eGFR up to 6 months later, with a mean change in eGFR of −0.4 mL/min/1.73 m^2 (95% CI, −4.9 to 4.0) associated with CTPA exposure. There was similarly no evidence for an association with need for kidney replacement therapy (risk difference [RD], 0.07%; 95% CI, −0.47% to 0.61%), mortality (RD, 0.3%; 95% CI, −2.9% to 3.2%), and acute kidney injury (RD, 4.3%; 95% CI, −2.7% to 12.9%), though the latter analysis was limited by missing data. Subgroup analyses were potentially consistent with harm among patients with diabetes (mean eGFR change −6.4 mL/min/1.73 m^2; 95% CI, −15.4 to 0.2), but not among those with other reported risk factors for contrast-induced nephropathy; these analyses, however, were relatively underpowered.

CONCLUSIONS AND RELEVANCE Using a cohort study design and analysis that permits stronger causal interpretation than existing observational research, we found no evidence for a harmful effect on kidney function of intravenous contrast administered for CTPA in an emergency setting.

Author Affiliations: Department of Epidemiology, Biostatistics and Occupational Health, Faculty of Medicine, McGill University, Montreal, Quebec, Canada (Goulden, Abrahamowicz, Strumpf, Tamblyn); Department of Emergency Medicine, Faculty of Medicine & Dentistry and School of Public Health, both at the University of Alberta, Edmonton, Alberta, Canada (Rowe); Department of Economics, Faculty of Arts, McGill University, Montreal, Quebec, Canada (Strumpf).

Corresponding Author: Robert Goulden, MBBS, Department of Epidemiology, Biostatistics and Occupational Health, McGill University, 1020 Pine Ave W, Montreal, Quebec H3A 1A2, Canada (robert.goulden@mail.mcgill.ca).

O ne of the most important reported harms of radiocontrast administration is acute kidney injury (AKI), an adverse effect known as contrast-induced nephropathy (CIN). A number of recent observational studies,[1-8] however, found no association between contrast exposure and adverse renal outcomes. These studies suggest that although CIN may have existed with contrast agents used in the past, modern agents and doses do not appear to be harmful.[9] The existing evidence, however, is limited by a number of potential biases. First, confounding may result from baseline differences in the risk of developing kidney injury between exposure groups. For example, individuals receiving noncontrast CT scans, often used as a comparator group, may be receiving such a scan because they are perceived to be at high risk of kidney injury. In addition, selection bias may arise because many existing studies look at acute kidney injury (AKI) as their outcome, and limit study inclusion to those with appropriately timed repeat creatinine measurements.[1,6-8] Although creatinine levels may be routinely measured after contrast exposure due to a belief in CIN, serial creatinine measurement in unexposed controls presumably reflects clinician beliefs that the patients have some other predisposition to AKI. These factors may contribute to forming a control group at high risk of kidney injury, creating a bias in favor of contrast and thus potentially masking harm. Despite several studies finding no evidence for CIN, their methodological limitations preclude clear casual interpretation and mean that concern over kidney injury from contrast exposure is still widespread among clinicians. As a result, important diagnostic imaging and procedures may be avoided due to fear of CIN, especially among patients with preexisting kidney impairment. To advance knowledge on this question, new analytical approaches that allow stronger causal interpretation are required.

Methods

The present study seeks to overcome the limitations of existing research by using the regression discontinuity design (RDD). The RDD approach relies on the existence of a continuous variable, the running variable, for which there is a cutoff that determines eligibility for receiving treatment. Individuals who fall just either side of the cutoff have markedly different probabilities of receiving the treatment, but are expected to have very similar values of other characteristics, including potential confounders.[10,11] By comparing outcomes in individuals just either side of the cutoff, the RDD approach can provide effect estimates from observational data that are largely free from both measured and unmeasured confounding.[12-16] In the case of intravenous contrast, this will be achieved by studying individuals receiving D-dimer testing (the running variable) in the emergency department (ED). The most common indication for this test is suspected pulmonary embolism (PE),[17,18] with those scoring above the cutoff—typically 500 ng/mL— more likely to receive contrast in the form of a computed tomographic pulmonary angiogram (CTPA) to rule in or rule out the diagnosis. Approval for this study was obtained from the Health Research Ethics Board of the University of Alberta

Key Points

Question Is intravenous radiocontrast associated with clinically significant kidney injury?

Findings In this quasi-experimental cohort study of 156 028 individuals, exposure to intravenous contrast was associated with a 0.4 mL/min/1.73 m² reduction in estimated glomerular filtration rate up to 6 months later, which was not statistically significant nor clinically meaningful.

Meaning Intravenous contrast was not associated with significant long-term kidney injury; the regression discontinuity design used in this study allows for greater confidence that this effect estimate is not distorted by confounding.

(Pro00091979), including a waiver for obtaining participant consent due to the deidentified and retrospective nature of the data.

Study Population and Data

The study population included all individuals aged 18 years or older who had a D-dimer measured during an ED visit in the Canadian province of Alberta between April 1, 2013 and June 30, 2018. Patients were excluded if they did not also have a baseline estimated glomerular filtration rate (eGFR) reported within 2 hours of the D-dimer result, or if they received kidney replacement therapy (dialysis or kidney transplantation) in the preceding 6 months. For individuals with eligible repeat visits, only the first visit was included.

Like all Canadian provinces, Alberta has universal publicly funded health care. Laboratory and imaging data from across the province, as well as patient demographics and clinical covariates, are stored in central Alberta Health Services data sets, and can be linked by a unique identifier. These include the laboratory, imaging, and discharge abstract data sets, and ED visit summaries.[19-21]

Outcome and Exposure Variables

The primary outcome was long-term kidney function, measured by eGFR up to 6 months after the index ED visit. Long-term kidney function is a more patient-centered outcome than AKI because it is more proximate to harder clinical end points such as permanent kidney replacement therapy. It also helps address the problem of selection bias that arises with using AKI as an outcome, as the indications for testing eGFR months after the ED visit are much less likely to be affected by variables associated with the initial probability of CTPA exposure. Where multiple eGFR measurements were taken in the 6 months after the index visit, the latest measurement was used. Secondary outcomes were receipt of kidney replacement therapy (dialysis or kidney transplantation) in the 6 months after the index ED visit, AKI—defined as an increase in creatinine levels of 50% or 0.3 mg/dL (26 μmol/L) within 7 days—and all-cause mortality at 6 months.

The primary exposure was receipt of CTPA during the index ED visit. Additional covariates that may be associated with the outcome were included in the statistical analyses to improve the precision of effect estimates.[22-24] These were age,

baseline eGFR, sex, diabetes, hypertension, cancer, coronary artery disease, ED triage score, and Charlson comorbidity index. Further details on these variables are provided in Exposure Variables in the Supplement.

Statistical Analysis

We used a fuzzy RDD analysis to estimate the association of CTPA exposure with long-term eGFR, with D-dimer as the running variable. Fuzzy RDD is a form of instrumental variable analysis, where the magnitude of the jump or discontinuity in the exposure that occurs at the cutoff is used to rescale any discontinuity in the outcome that occurs at the cutoff.[25] This maintains the unconfounded effect estimate of the RDD approach while accounting for imperfect compliance with the treatment cutoff. The resulting effect estimate is the complier average causal effect, which is the effect of the intervention among those whose treatment allocation is determined by the cutoff (compliers).[11]

For each outcome, we report both the intention-to-treat (ITT) effect of crossing the D-dimer cutoff, and the rescaled complier average causal effect attributable to CTPA itself. For the primary outcome, the effect estimate will be the difference in long-term eGFR, whereas for the binary secondary outcomes, it will be the risk difference (RD). The associations between the running variable and both (1) the exposure and (2) the outcome were evaluated using local linear regression, with separate regression lines fitted above and below the cutoff.[26,27] The difference in where these lines intersect the cutoff quantify the discontinuity in the exposure and outcome.[16] The local linear approach minimizes bias by limiting the study sample to a defined bandwidth around the cutoff in which a linear regression can be estimated. This reduces the risk of misspecification errors that may arise from the more complex functional forms that are needed to fit the regression curve across the whole range of the running variable values.[28] The size of the bandwidth, which was allowed to vary above vs below the cutoff, was automatically selected using a data-driven method that seeks to optimally balance the bias-variance trade off.[29,30] We used an asymmetric bandwidth as we anticipated an asymmetric distribution of the running variable, D-dimer, and optimization of the bias-variance trade off may vary for the different regression slopes on either side of the cutoff. A triangular kernel was used, such that individuals closest to the cutoff were more heavily weighted than those further away. To account for potential misspecification of the regression function and the additional variance that this generates, bias-adjusted robust CIs were estimated.[31,32]

Although in most hospitals in the study, a D-dimer cutoff of 500 ng/mL was considered a positive result, some used 460 ng/mL or 470 ng/mL as the cutoff.[33,34] All participants therefore had their D-dimer centered on whichever cutoff was used in the institution of their index ED visit. Individuals whose D-dimer fell exactly on the cutoff were excluded from analysis because their classification with regard to the cutoff is ambiguous and may thus result in distortion of the treatment discontinuity.

Additional analyses were performed to assess the sensitivity of results to bandwidth size and symmetry, along with global (ie, whole data set) analyses using polynomials of varying degrees. Subgroup analyses were carried out to explore if the effect of treatment varied between groups considered to be at high and low risk of CIN,[35] using the method of Altman and Bland.[36] Finally, we performed an analysis using all eGFR measurements between 7 days and 6 months after the index ED visit as the outcome, with a variance estimator robust to clustering by participant,[37] to determine if this could improve the precision of our effect estimates. Details of these additional analyses are provided in Supplementary Analyses in the Supplement.

All analyses were limited to complete cases. As a retrospective study relying on routinely collected clinical data, there may be significant missing data for the primary outcome of long-term eGFR and secondary outcome of AKI. We assessed whether this may give rise to selection bias by evaluating if (1) the frequency of missingness and (2) timing of data collection, changed at the cutoff. If there was no association between treatment group and data missingness, as evidenced by no change at the cutoff, this would provide confidence that the use of a complete case analysis would not result in marked selection bias. This reflects the fact that selection bias requires the existence of an association between study inclusion and treatment group.[38] In contrast because Alberta has universal health care and administrative data should capture all episodes of new dialysis, kidney transplant, or death, these outcomes should have no missing data except for patients who move out of province.

All analyses were performed using Stata statistical software (version 15, Stata Corp), with the primary and secondary analyses using the rdrobust package.[37] Two-sided alpha was set at 0.05. The code used in the statistical analysis is available at https://github.com/goulden/contrast.

Table 1. Characteristics of Individuals Undergoing Emergency Department D-Dimer Testing

Variable	Value (%)	Discontinuity at the D-dimer cutoff
Age, mean (SD), y	53 (19)	0.02
Male	44	1.6%
Baseline eGFR, mean (SD), mL/min/1.73 m²	86 (26)	0.07
Diabetes	12	0.03%
Hypertension	13	−1.8%
Coronary artery disease	5	−0.1%
Cancer	3	0.3%
CTAS score		
1-2	40	
3	45	0.04
4-5	15	
Charlson comorbidity index score		
0	71	
1	16	
2	7	0.002
≥3	7	

Abbreviations: CTAS, Canadian Triage and Acuity Scale; eGFR, estimated glomerular filtration rate.

Figure 1. Association Between D-Dimer and Primary Exposure and Potential Confounders
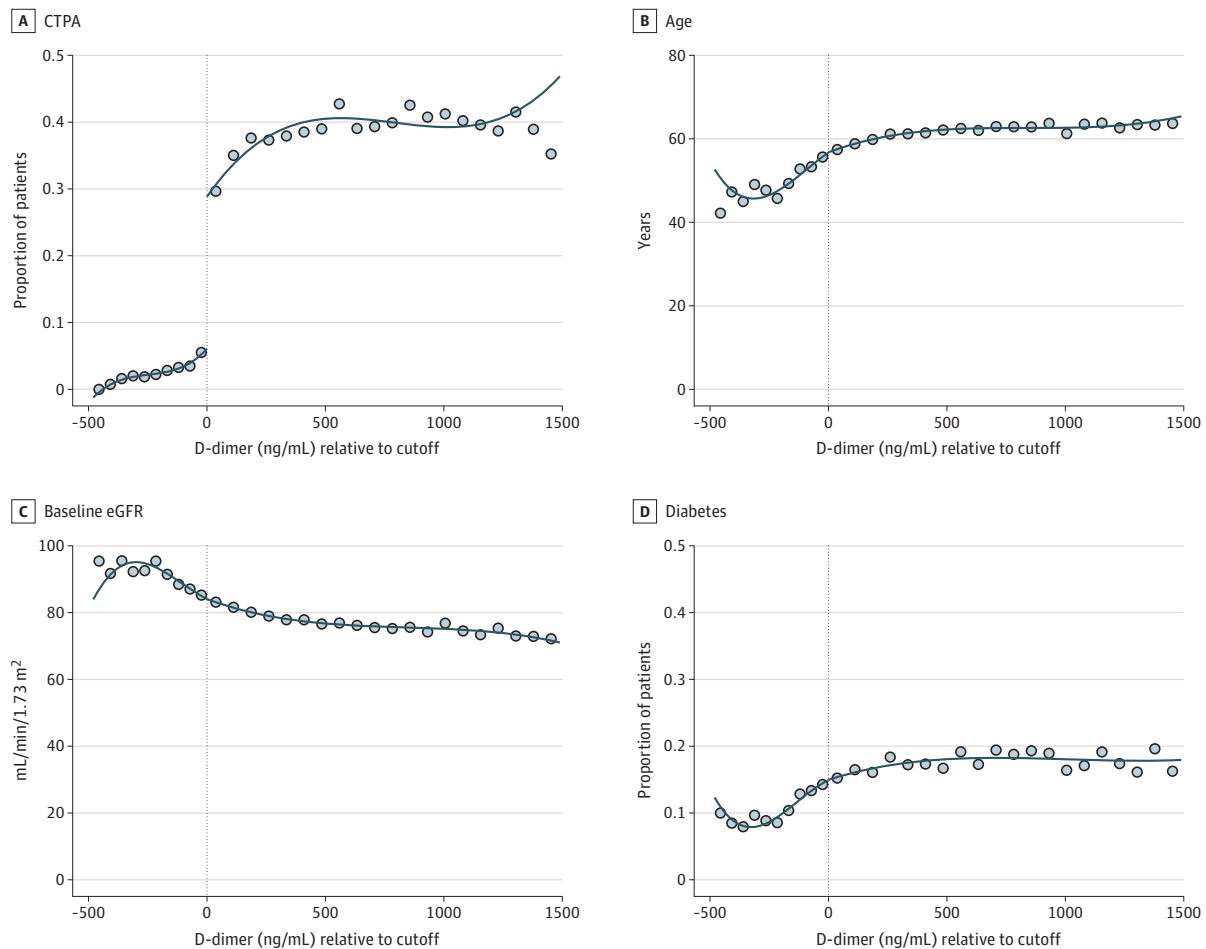
A, Primary exposure. B, C, and D, Potential confounders. The blue circles represent the mean value for individual patients and the dotted lines indicate the D-dimer cutoff. CTPA indicates computed tomographic pulmonary angiogram; eGFR, estimated glomerular filtration rate.

Results

There were 156 028 individuals who received a D-dimer test and met inclusion criteria during the study period (eFigure 1 in the Supplement). Patient characteristics are described in **Table 1**. The mean age was 53 years, 68 206 (44%) were men and 87 822 (56%) were women, and the mean baseline eGFR was 86 mL/min/1.73 m^2. eTable 1 in the Supplement groups patients by CTPA receipt, demonstrating between group differences that may lead to confounding if analyzed using conventional methods. The association between D-dimer and receipt of CTPA, as well as several potential confounders, is depicted in **Figure 1** and eFigure 2 in the Supplement. This demonstrates a clear 23% discontinuity in CTPA exposure at the D-dimer cutoff. There is no evidence of any discontinuity for potential confounders (Table 1), meaning that exposure groups were well balanced at the cutoff, corroborating the assumptions underlying the RDD analysis.

Data on the primary outcome, long-term eGFR, was available for 84 624 patients (54%) (eTable 2 in the Supple-

ment). The frequency of missing eGFR measurements and their timing did not change at the cutoff (eTable 3, eFigure 3 in the Supplement). The median time to the last eGFR test in the 6 months following the ED visit was 3.7 months (interquartile range, 1.8-5.1). Bandwidths of 80 ng/mL below and 1190 ng/mL above the cutoff were automatically selected by the software package, within which 29 830 patients were included. The estimated ITT effect of the D-dimer cutoff on long-term eGFR is depicted in **Figure 2**A, with a nonsignificant discontinuity of −0.1 mL/min/1.73 m^2 (95% CI, −1.2 to 1.1) (**Table 2**).

In the local linear fuzzy RDD analysis, there was no evidence of an association of intravenous contrast with longterm eGFR, with an eGFR change of −0.4 mL/min/1.73 m^2 (95% CI, −4.9 to 4.0) attributable to CTPA exposure caused by crossing the D-dimer cutoff (Table 2). A sensitivity analysis including all 84 624 patients and using a global cubic polynomial fuzzy RDD approach similarly found no evidence of an association, with an eGFR change of 0.4 mL/min/1.73 m^2 (95% CI, −2.1 to 2.8) attributable to CTPA exposure (Figure 2B; eTable 4 in the Supplement). Of 8 sensitivity analyses using different

Figure 2. Association Between D-Dimer and Long-term eGFR
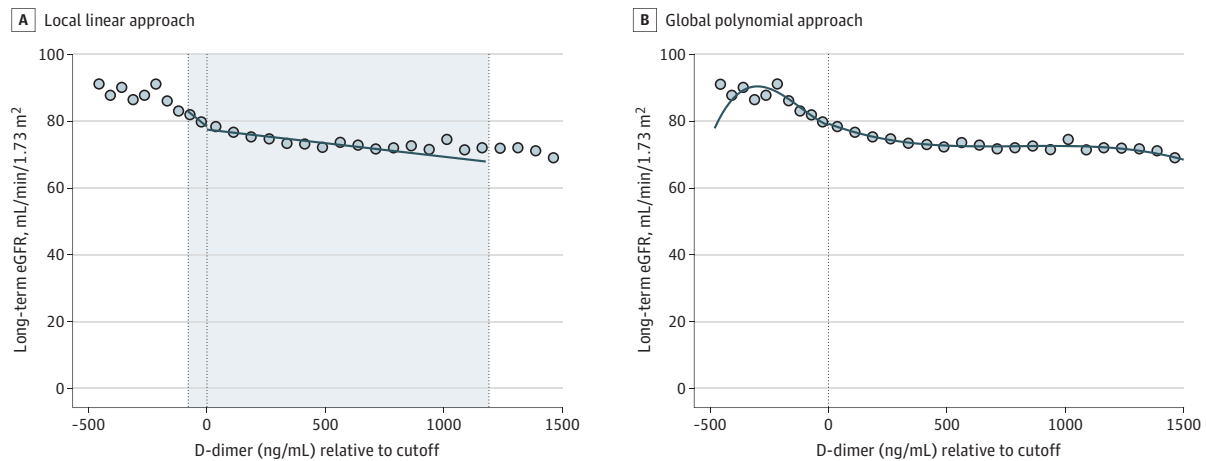
A, Using a local linear approach. B, Using a global polynomial approach. The blue circles represent the mean value for individual patients, and the dotted lines indicate the D-dimer cutoff and the shaded area shows the local linear regression bandwidth. eGFR indicates estimated glomerular filtration rate.

bandwidths and polynomial orders, 7 found no evidence of an association (eTable 4 in the Supplement).

Overall, 165 (0.11%) patients required kidney replacement therapy during the 6 months following their ED visit (161 dialysis, 4 kidney transplant). There was no evidence of an association of CTPA exposure with the need for kidney replacement therapy (RD, 0.07% [95% CI, −0.47% to 0.61%]) (Table 2; eFigure 4A in the Supplement). Of those with repeat creatinine levels measured within 7 days, 4147 (9.7%) developed AKI, with no evidence of an association of contrast exposure with this risk (RD, 4.3% [95% CI, −2.7% to 12.9%]) (Table 2; eFigure 4B in the Supplement). However, repeated creatinine measurements within 7 days were only available for 42 691 patients (27%), with a discontinuity in missingness at the cutoff (eTable 3, eFigure 5A in the Supplement). Overall, 6656 patients (4.3%) died in the 6 months following the index ED visit, with no evidence of an association with CTPA (RD, 0.3% [95% CI, −2.9% to 3.2%]).

Subgroup analyses (Table 3) found no evidence that the association of contrast with long-term eGFR varied by baseline eGFR, age, or hypertension. Among those with diabetes, the association was potentially consistent with harm although not statistically significant, with an eGFR change of −6.4 mL/min/1.73 m^2 (95% CI, −15.4 to 0.2; P for heterogeneity = .12). In a sensitivity analysis using all eGFR measurement 7 days to 6 months after the index ED visit as the outcome, CTPA exposure was associated with an eGFR change of −0.9 mL/min/1.73 m^2 (95% CI, −7.6 to 2.4).

Discussion

In this large, multiyear study using population-based data, we found no evidence for an association of intravenous contrast with kidney function measured by eGFR up to 6 months after exposure to CTPA. There was similarly no evidence of an association with the risk of renal replacement therapy, all-cause mortality, or AKI, though the latter analysis was lim-

Table 2. Effect of D-Dimer Cutoff (ITT) and CTPA Exposure (Complier Average Causal Effect) on Primary and Secondary Outcomes

Outcome	Population mean	eGFR, difference (95% CI)
Primary outcomes		
Long-term eGFR, mL/min/1.73 m^2		
D-dimer cutoff	80.9	−0.1 (−1.2 to 1.1)
CTPA		−0.4 (−4.9 to 4.0)
Secondary outcomes, risk difference, % (95% CI)		
Renal replacement therapy		
D-dimer cutoff	0.11	0.07 (−0.03 to 0.19)
CTPA		0.07 (−0.47 to 0.61)
Acute kidney injury		
D-dimer cutoff	9.7	0.9 (−0.5 to 3.0)
CTPA		4.3 (−2.7 to 12.9)
All-cause mortality		
D-dimer cutoff	4.3	0.1 (−0.7 to 0.8)
CTPA		0.3 (−2.9 to 3.2)

Abbreviations: CTPA, computed tomography pulmonary angiogram; eGFR, estimated glomerular filtration rate; ITT, intention-to-treat.

ited by missing data. Results were consistent across most subgroups thought to be at elevated risk of CIN, although these analyses were relatively underpowered.

Definitively proving a negative is difficult, but the results of our study suggest that a clinically significant association of intravenous contrast with long-term renal function is very unlikely. The lower 95% CI of our primary outcome, an eGFR drop of 4.9 mL/min/1.73 m^2, is less than one-fifth of a standard deviation of baseline eGFR and of limited clinical significance. Furthermore, the point estimates in our primary analysis and in 6 of the 8 sensitivity analyses (eTable 4 in the Supplement) yielded an eGFR difference (positive or negative) of less than 1.5 mL/min/1.73 m^2 attributable to CTPA. On the other hand, for our secondary outcomes of AKI and renal replacement therapy, it is more challenging to reject the possibility of an

Table 3. Effect of CTPA Exposure on Long-term eGFR by Subgroup

Variable	eGFR difference (95% CI), mL/min/1.73 m²	P value for heterogeneity
Overall effect estimate	−0.4 (−4.9 to 4.0)	NA
Baseline eGFR, mL/min/1.73m²		
≥45	−3.6 (−9.5 to 1.8)	.74
<45	0.5 (−12.1 to 33.8)	
Age, y		
<60	0 (−5.3 to 5.7)	.62
≥60	−2.1 (−9.2 to 3.7)	
Diabetes		
No	0.8 (−4.0 to 5.9)	.12
Yes	−6.4 (−15.4 to 0.2)	
Hypertension		
No	−0.2 (−5.1 to 5.0)	.82
Yes	−1.3 (−9.9 to 6.4)	

Abbreviations: CTPA, computed tomography pulmonary angiogram; eGFR, estimated glomerular filtration rate; NA, not applicable.

association. Although the difference was not statistically significant, the point estimate and upper 95% CI of the AKI outcome were consistent with a clinically significant association. However, this analysis may be at risk of selection bias (eTable 3 in the Supplement), and the null effect of the primary analysis suggests that if there was any acute kidney injury it did not progress to long-term injury. The point estimate and upper 95% CI of the kidney replacement therapy outcome were very small in absolute terms, though a clinically relevant relative effect could not be excluded.

In our subgroup analyses of potentially high-risk patients, none of the stratum-specific effect estimates or tests of heterogeneity led us to reject the null hypothesis of no effect. However, these analyses were relatively underpowered. The point estimates for most potentially high-risk subgroups—those with eGFR lower than 45 mL/min/1.73 m², older than 60 years, or hypertension—were very small, although their CIs included potentially clinically significant effects. The point estimate for patients with diabetes, however, was potentially compatible with clinically significant harm. Despite being an independent risk factor for acute and chronic kidney injury, most existing studies do not find evidence that diabetes specifically increases the risk of CIN.[39-41] However, given the risk of residual confounding in existing research, and our finding consistent with possible harm, further research using causally robust methodology is warranted in this subgroup.

These findings are consistent with a number of existing studies[1-5] finding no association between intravenous contrast and kidney injury. However, our quasi-experimental design allows for causal interpretation with much greater confidence than existing research. At the D-dimer cutoff, there was no evidence of discontinuities in any of the measured confounders, analogous to a well-balanced randomized clinical trial, lending support to the idea that the same is true for unmeasured confounders.

An additional benefit of our study was the ability to evaluate the risk of selection bias. Unlike many other studies that limit inclusion to those with repeated creatinine measurements,[1,6-8]

our inclusion criteria were based solely on baseline characteristics. Although we performed complete case analyses, we were able to evaluate the risk of selection bias by exploring the association between the D-dimer cutoff and the risk of missing data (and hence exclusion from the analysis). The absence of a discontinuity in missingness means there is no association between exposure group and study inclusion, significantly reducing the possibility of selection bias.[38] Of note, we did find evidence for an association between exposure status and outcome measurement for our secondary outcome of AKI, raising a concern for selection bias in studies that limit inclusion to those with repeat short-term creatinine measurements. Although there was no evidence of a discontinuity in missingness for our primary outcome, it remains possible that CTPA exposure would increase eGFR retesting for some (eg, by causing AKI) and decrease it for others (eg, by causing mortality), thus potentially giving rise to selection bias despite no detectable discontinuity in outcome missingness.

Additional strengths of our study include the large sample size, comprising more participants that the total number in a recent meta-analysis[5] on this question, and the use of a comprehensive population-wide data set, maximizing representativeness, and providing near complete outcome ascertainment for the kidney replacement therapy and mortality outcomes.

Limitations

The principal limitation of any RDD analysis relates to the generalizability of the results. Because the treatment effect is estimated for those whose D-dimer value falls at the cutoff, it may not apply to those further away from this value. Because this is a fuzzy RDD analysis, the treatment effect is further restricted to those at the cutoff who are compliers ie, those whose receipt of a contrast-enhanced scan is determined by the cutoff. Individuals perceived to be at higher risk of kidney injury are less likely to have their CTPA receipt determined primarily by their D-dimer results, thus may be underrepresented among compliers. However, supplementary analyses found no evidence of heterogeneity of the treatment effect between compliers and noncompliers (Supplementary Analyses and eFigure 6 in the Supplement).

An additional potential limitation is violation of the exclusion restriction, whereby exposures other than intravenous contrast are affected by crossing the cutoff. It is likely that in patients perceived to be at high risk of kidney injury, clinicians would have taken steps to mitigate this risk, such as prescribing prophylactic prehydration. It was not possible to evaluate this directly because treatment data was not available in our data set. Whether such mitigation strategies would have masked any harm from contrast is called into question, however, by multiple randomized clinical trials[42-45] showing no effect of these therapies on the risk of postcontrast AKI.

Conclusions

To our knowledge, this study provides the strongest evidence to date that intravenous contrast is not associated with significant kidney injury, further challenging the considerable clinical preoccupation with the occurrence and prevention of CIN.

REFERENCES

1. Hinson JS, Ehmann MR, Fine DM, et al. Risk of acute kidney injury after intravenous contrast media administration. *Ann Emerg Med*. 2017;69(5):577-586.e4. doi:10.1016/j.annemergmed.2016.11.021

2. Miyamoto Y, Iwagami M, Aso S, et al. Association between intravenous contrast media exposure and non-recovery from dialysis-requiring septic acute kidney injury: a nationwide observational study. *Intensive Care Med*. 2019;45(11):1570-1579. doi:10.1007/s00134-019-05755-2

3. Williams LS, Walker GR, Loewenherz JW, Gidel LT. Association of contrast and acute kidney injury in the critically ill: a propensity-matched study. *Chest*. 2020;157(4):866-876. doi:10.1016/j.chest.2019.10.005

4. STARSurg Collaborative. Perioperative intravenous contrast administration and the incidence of acute kidney injury after major gastrointestinal surgery: prospective, multicentre cohort study. *BJS Br J Surg*. 2020;107(8):1023-1032. doi:10.1002/bjs.11453

5. Aycock RD, Westafer LM, Boxen JL, Majlesi N, Schoenfeld EM, Bannuru RR. Acute kidney injury after computed tomography: a meta-analysis. *Ann Emerg Med*. 2018;71(1):44-53.e4. doi:10.1016/j.annemergmed.2017.06.041

6. Heller M, Krieger P, Finefrock D, Nguyen T, Akhtar S. Contrast CT scans in the emergency department do not increase risk of adverse renal outcomes. *West J Emerg Med*. 2016;17(4):404-408. doi:10.5811/westjem.2016.4.28994

7. Sonhaye L, Kolou B, Tchaou M, et al. Intravenous contrast medium administration for computed tomography scan in emergency: a possible cause of contrast-induced nephropathy. *Radiol Res Pract*. 2015;2015:805786. doi:10.1155/2015/805786

8. Bruce RJ, Djamali A, Shinki K, Michel SJ, Fine JP, Pozniak MA. Background fluctuation of kidney function versus contrast-induced nephrotoxicity. *AJR Am J Roentgenol*. 2009;192(3):711-718. doi:10.2214/AJR.08.1413

9. Mehran R, Dangas GD, Weisbord SD. Contrast-associated acute kidney injury. *N Engl J Med*. 2019;380(22):2146-2155. doi:10.1056/NEJMra1805256

10. Bor J, Moscoe E, Mutevedzi P, Newell M-L, Bärnighausen T. Regression discontinuity designs in epidemiology: causal inference without randomized trials. *Epidemiology*. 2014;25(5):729-737. doi:10.1097/EDE.0000000000000138

11. Oldenburg CE, Moscoe E, Bärnighausen T. Regression discontinuity for causal effect estimation in epidemiology. *Curr Epidemiol Rep*. 2016;3:233-241. doi:10.1007/s40471-016-0080-x

12. Moscoe E, Bor J, Bärnighausen T. Regression discontinuity designs are underutilized in medicine, epidemiology, and public health: a review of current and best practice. *J Clin Epidemiol*. 2015;68(2):122-133. doi:10.1016/j.jclinepi.2014.06.021

13. Venkataramani AS, Bor J, Jena AB. Regression discontinuity designs in healthcare research. *BMJ*. 2016;352:i1216. doi:10.1136/bmj.i1216

14. Maas IL, Nolte S, Walter OB, et al. The regression discontinuity design showed to be a valid alternative to a randomized controlled trial for estimating treatment effects. *J Clin Epidemiol*. 2017;82:94-102. doi:10.1016/j.jclinepi.2016.11.008

15. van Leeuwen N, Lingsma HF, Mooijaart SP, Nieboer D, Trompet S, Steyerberg EW. Regression discontinuity was a valid design for dichotomous outcomes in three randomized trials. *J Clin Epidemiol*. 2018;98:70-79. doi:10.1016/j.jclinepi.2018.02.015

16. Maciejewski ML, Basu A. Regression discontinuity design. *JAMA*. 2020;324(4):381-382. doi:10.1001/jama.2020.3822

17. Arnason T, Wells PS, Forster AJ. Appropriateness of diagnostic strategies for evaluating suspected venous thromboembolism. *Thromb Haemost*. 2007;97(2):195-201. doi:10.1160/TH06-10-0596

18. Parry BA, Chang AM, Schellong SM, et al. International, multicenter evaluation of a new D-dimer assay for the exclusion of venous thromboembolism using standard and age-adjusted cut-offs. *Thromb Res*. 2018;166:63-70. doi:10.1016/j.thromres.2018.04.003

19. Alberta Health Services. Alberta Health Services Data Repository for Reporting (AHSDRR) and Data Stores Data Asset Inventory. 2016. Accessed March 15, 2020. https://cloudfront.ualberta.ca/-/media/medicine/research/faculty/clin-res/spor-available-datasets.pdf

20. Canadian Institute for Health Information. Data Quality Documentation, Discharge Abstract Database.; 2019. Accessed March 15, 2020. https://www.cihi.ca/sites/default/files/document/current-year-information-dad-2018-2019-en-web.pdf

21. Canadian Institute for Health Information. Data Quality Documentation, National Ambulatory Care Reporting System.; 2019. Accessed March 15, 2020. https://www.cihi.ca/sites/default/files/document/current-year-information-nacrs-2018-2019-en-web.pdf

22. Kahan BC, Jairath V, Doré CJ, Morris TP. The risks and rewards of covariate adjustment in randomized trials: an assessment of 12 outcomes from 8 studies. *Trials*. 2014;15:139. doi:10.1186/1745-6215-15-139

23. Calonico S, Cattaneo M, Farrell MH, Titiunik R. Regression discontinuity designs using covariates. *Rev Econ Stat*. 2019;101(3):442-451. doi:10.1162/rest_a_00760

24. Bland JM, Altman DG. Best (but oft forgotten) practices: testing for treatment effects in randomized trials by separate analyses of changes from baseline in each group is a misleading approach. *Am J Clin Nutr*. 2015;102(5):991-994. doi:10.3945/ajcn.115.119768

25. Imbens GW, Lemieux T. Regression discontinuity designs: a guide to practice. *J Econom*. 2008;142(2):615-635. doi:10.1016/j.jeconom.2007.05.001

26. Cattaneo MD, Idrobo N, Titiunik R. *A Practical Introduction to Regression Discontinuity Designs: Foundations.* Cambridge University Press; 2020.

27. Hahn J, Todd P, Van der Klaauw W. Identification and estimation of treatment effects with a regression-discontinuity design. *Econometrica*. 2001;69(1):201-209. doi:10.1111/1468-0262.00183

28. Jacob R, Zhu P, Somers M-A, Bloom H. A Practical Guide to Regression Discontinuity. MDRC; 2012. Accessed July 3, 2020. https://www.mdrc.org/sites/default/files/RDD%20Guide_Full%20rev%202016_0.pdf

29. Cattaneo MD, Idrobo N, Titiunik R. The Continuity-Based Approach to RD Analysis. *A Practical Introduction to Regression Discontinuity Designs: Foundations.* Cambridge University Press; 2020.

30. Calonico S, Cattaneo MD, Farrell MH. Optimal bandwidth choice for robust bias corrected inference in regression discontinuity designs. *Econom J.* 2020;23(2):192-210. doi:10.1093/ectj/utz022

31. Calonico S, Cattaneo MD, Titiunik R. Robust nonparametric confidence intervals for regression-discontinuity designs. *Econometrica*. 2014;82(6):2295-2326. doi:10.3982/ECTA11757

32. Calonico S, Cattaneo MD, Titiunik R. Robust data-driven inference in the regression-discontinuity design. *Stata J.* Published online December 1, 2014. doi:10.1177/1536867X1401400413

33. Alberta Health Services. Laboratory Bulletin - Quantitative D-Dimer Test.; 2012. Accessed August 1, 2020. https://www.albertahealthservices.ca/assets/wf/lab/wf-lab-quantitative-d-dimer-testing.pdf

34. Senior K, Burles K, Wang D, et al. Age-adjusted D-dimer thresholds in the investigation of suspected pulmonary embolism: a retrospective

evaluation in patients ages 50 and older using administrative data. *CJEM*. 2018;20(5):725-731. doi:10.1017/cem.2018.389

35. ACR Committee on Drugs and Contrast Media. ACR Manual on Contrast Media. American College of Radiology; 2020. Accessed July 3, 2020. https://www.acr.org/Clinical-Resources/Contrast-Manual

36. Altman DG, Bland JM. Interaction revisited: the difference between two estimates. *BMJ*. 2003; 326(7382):219. doi:10.1136/bmj.326.7382.219

37. Calonico S, Cattaneo MD, Farrell MH, Titiunik R. Rdrobust: software for regression-discontinuity designs: *Stata J*. Published online June 1, 2017. doi:10.1177/1536867X1701700208

38. Hernán MA, Hernández-Díaz S, Robins JM. A structural approach to selection bias. *Epidemiology*. 2004;15(5):615-625. doi:10.1097/01.ede.0000135174.63482.43

39. McDonald JS, McDonald RJ, Comin J, et al. Frequency of acute kidney injury following intravenous contrast medium administration:

a systematic review and meta-analysis. *Radiology*. 2013;267(1):119-128. doi:10.1148/radiol.12121460

40. McDonald RJ, McDonald JS, Carter RE, et al. Intravenous contrast material exposure is not an independent risk factor for dialysis or mortality. *Radiology*. 2014;273(3):714-725. doi:10.1148/radiol.14132418

41. Ellis JH, Khalatbari S, Yosef M, Cohan RH, Davenport MS. Influence of clinical factors on risk of contrast-induced nephrotoxicity from IV iodinated low-osmolality contrast material in patients with a low estimated glomerular filtration rate. *AJR Am J Roentgenol*. 2019;213(5):W188-W193. doi:10.2214/AJR.19.21424

42. Nijssen EC, Rennenberg RJ, Nelemans PJ, et al. Prophylactic hydration to protect renal function from intravascular iodinated contrast material in patients at high risk of contrast-induced nephropathy (AMACING): a prospective, randomised, phase 3, controlled, open-label, non-inferiority trial. *Lancet*. 2017;389(10076): 1312-1322. doi:10.1016/S0140-6736(17)30057-0

43. Timal RJ, Kooiman J, Sijpkens YWJ, et al. Effect of no prehydration vs sodium bicarbonate prehydration prior to contrast-enhanced computed tomography in the prevention of postcontrast acute kidney injury in adults with chronic kidney disease: the Kompas Randomized Clinical Trial. *JAMA Intern Med*. 2020;180(4):533-541. doi:10.1001/jamainternmed.2019.7428

44. Valette X, Desmeulles I, Savary B, et al. Sodium bicarbonate versus sodium chloride for preventing contrast-associated acute kidney injury in critically ill patients: a randomized controlled trial. *Crit Care Med*. 2017;45(4):637-644. doi:10.1097/CCM.0000000000002267

45. Kooiman J, Sijpkens YWJ, van Buren M, et al. Randomised trial of no hydration vs. sodium bicarbonate hydration in patients with chronic kidney disease undergoing acute computed tomography-pulmonary angiography. *J Thromb Haemost*. 2014;12(10):1658-1666. doi:10.1111/jth.12701

Supplemental Online Content

Goulden R, Rowe BH, Abrahamowicz M, Strumpf E, Tamblyn R. Association of intravenous radiocontrast with kidney function: a regression discontinuity analysis. *JAMA Intern Med*. Published online April 5, 2021. doi:10.1001/jamainternmed.2021.0916

Exposure variables

Supplementary analyses

This supplemental material has been provided by the authors to give readers additional information about their work.

Exposure variables

Age and baseline eGFR were modelled using restricted cubic splines. Sex, diabetes, hypertension, cancer, and coronary artery disease were modelled as binary variables. Finally, the Canadian Triage and Acuity Scale (CTAS) score from the index ED visit and Charlson comorbidity index (with values ≥5 grouped into one) were modelled as linear. Co-morbidity data were based on diagnoses present in National Ambulatory Care Reporting System (NACRS) ED visit summaries or the discharge abstract dataset for the index ED visit or any healthcare visit in the preceding 6 months.

Supplementary analyses

Alternate bandwidth sizes

Symmetric bandwidths of various sizes were used to assess the sensitivity of the local linear regression result to bandwidth symmetry and size, along with 'global' RDD analyses (including the whole dataset) using different polynomial orders and conventional inference methods. See eTable 3 for results.

Comparison of compliers to non-compliers

We evaluated if the effect among compliers could be generalized to non-compliers (i.e. those whose CTPA exposure was not determined by the cutoff), by using the F-test described by Bertanha and Imbens[1]. We found no evidence of heterogeneity of treatment effect, with the F-statistic p = 0.62. See also eFigure 6.

Use of all eGFR outcome values

We performed an analysis using all eGFR outcome measurements between 7 days and 6 months post index ED visit, as opposed to just the last measurement, to determine if this would improve the precision of our estimates. We used the same fuzzy RDD as our primary analysis, but included all outcome measures, and a cluster-robust variance estimator with each subject defined as a cluster[2]. The results of this analysis are reported in the main text.

Supplementary tables

eTable 1
Characteristics of individuals by CTPA receipt

	CTPA		
	No **N=131,753**	**Yes** **N=24,275**	**Total** **N=156,028**
Age, mean (SD)	52 (19)	60 (18)	53 (19)
Male	44%	45%	44%
Baseline eGFR (mL/min/1.73m^2), mean (SD)	87 (26)	82 (23)	86 (26)
Diabetes	12%	14%	12%
Hypertension	12%	16%	13%
Coronary artery disease	5%	6%	5%
Cancer	3%	8%	3%
CTAS			
1-2	38%	48%	40%
3	45%	44%	45%
4-5	17%	8%	15%
Charlson co-morbidity index			
0	73%	61%	71%
1	15%	20%	16%
2	6%	9%	7%
≥3	6%	11%	7%

Abbreviations: CTPA, computed tomography pulmonary angiogram; eGFR, estimated glomerular filtration rate; CTAS, Canadian Triage and Acuity Scale.

eTable 2
Variables with missing data

Variable	Missing (%)
Long-term eGFR	46%
Acute kidney injury	73%
Canadian Triage and Acuity Scale	1%

Complete data was available for all other variables.
Abbreviations: eGFR, estimated glomerular filtration rate.

eTable 3
Difference in missingness and timing of outcome measurements at the D-dimer cutoff

	Difference in prevalence of missingness (95% CI)
Long-term eGFR	-0.5% (-3.3 to 3.2%)
Acute kidney injury	-2.7% (-4.6 to -0.5%)
	Difference in timing of measurement (95% CI)
Long-term eGFR	0.7 days (-2.1 to 3.9 days)
Acute kidney injury	1.5 hours (-2.0 to 3.9 hours)

Abbreviations: eGFR, estimated glomerular filtration rate; CTAS, Canadian Triage and Acuity Scale.

eTable 4

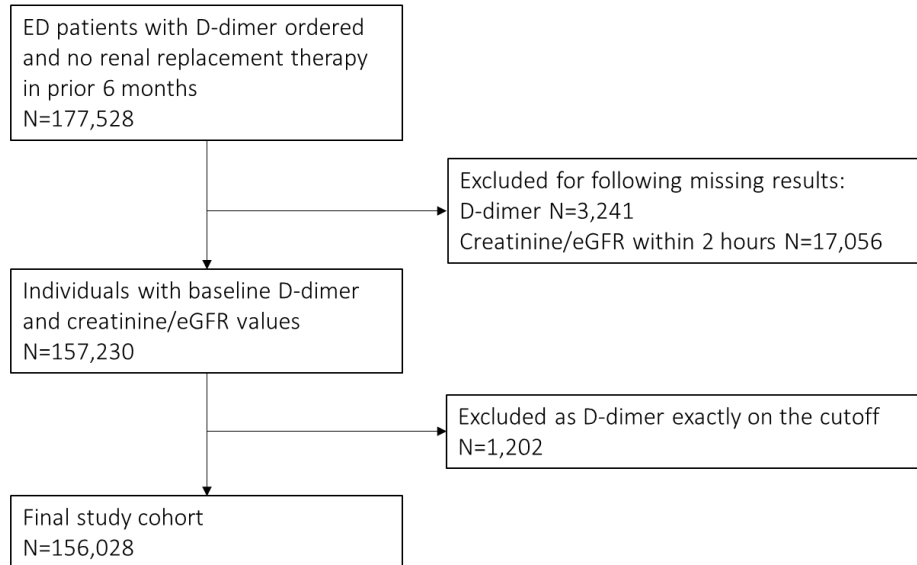Effect of CTPA exposure on long-term eGFR using different bandwidths

Bandwidth size (above and below)	CTPA effect on long-term eGFR (95% CI)
Local linear regression with varying bandwidths	
50 ng/ml	-9.3 (-36.4 to 15.4)
100 ng/ml	0.8 (-18.7 to 3.9)
250 ng/ml	1.4 (-3.9 to 6)
500 ng/ml	-0.6 (-1.6 to 4.6)
Global regression using varying polynomial degrees	
2	1.2 (-0.5 to 2.8)
3	0.4 (-2.1 to 2.8)
4	-3.7 (-7 to -0.4)
5	0.7 (-3.8 to 5.2)

Abbreviations: CTPA, computed tomography pulmonary angiogram; eGFR, estimated glomerular filtration rate.
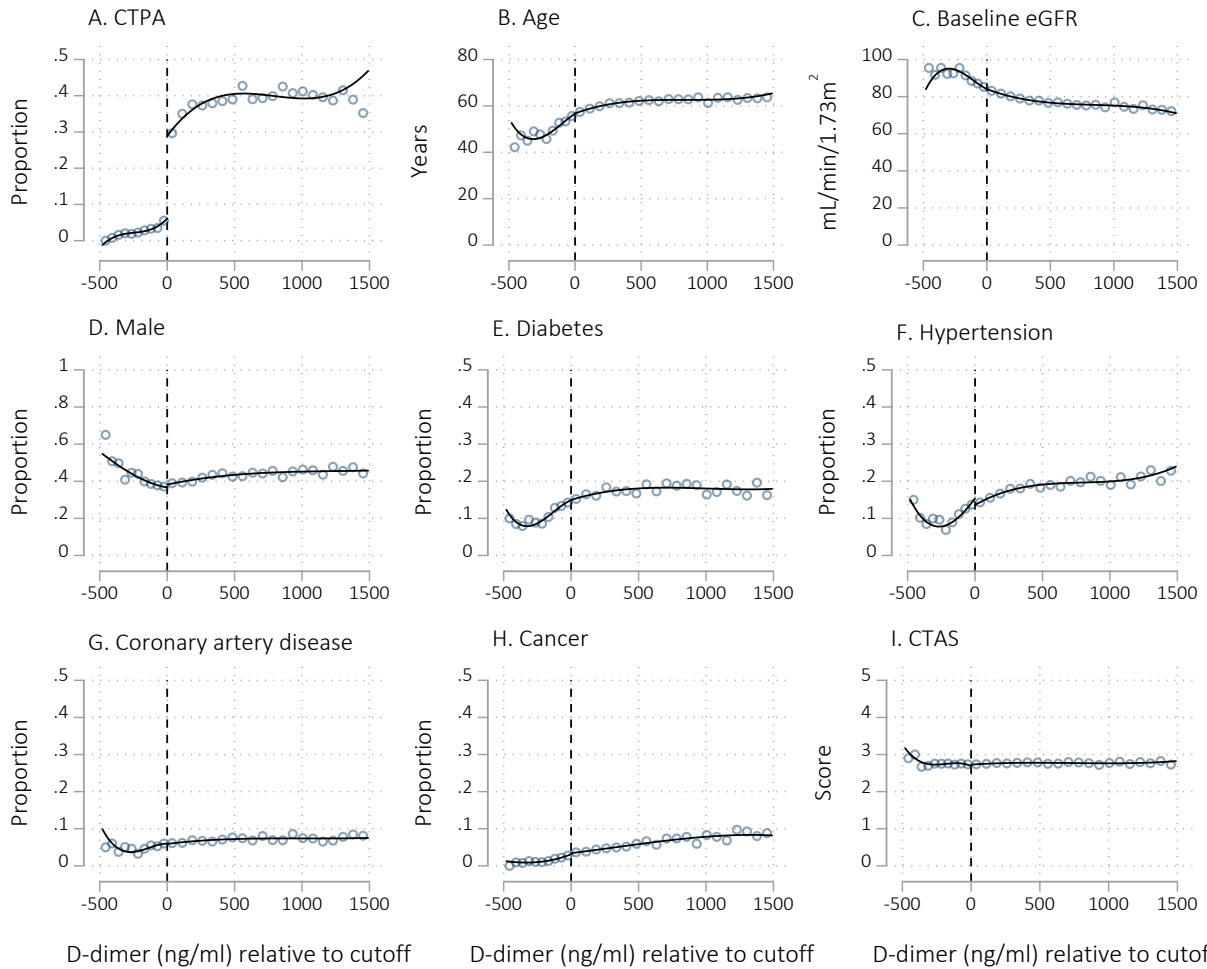
Supplementary figures

eFigure 1
Participant inclusion flow diagram

ED patients with D-dimer ordered and no renal replacement therapy in prior 6 months N=177,528

→ | Excluded for following missing results:
D-dimer N=3,241
Creatinine/eGFR within 2 hours N=17,056 |

Individuals with baseline D-dimer and creatinine/eGFR values N=157,230

→ | Excluded as D-dimer exactly on the cutoff
N=1,202 |

Final study cohort N=156,028

eFigure 2

Association between D-dimer and primary exposure (A) and potential confounders (B-I)

Abbreviations: CTPA, computed tomography pulmonary angiogram; eGFR, estimated glomerular filtration rate; CTAS, Canadian Triage and Acuity Scale.
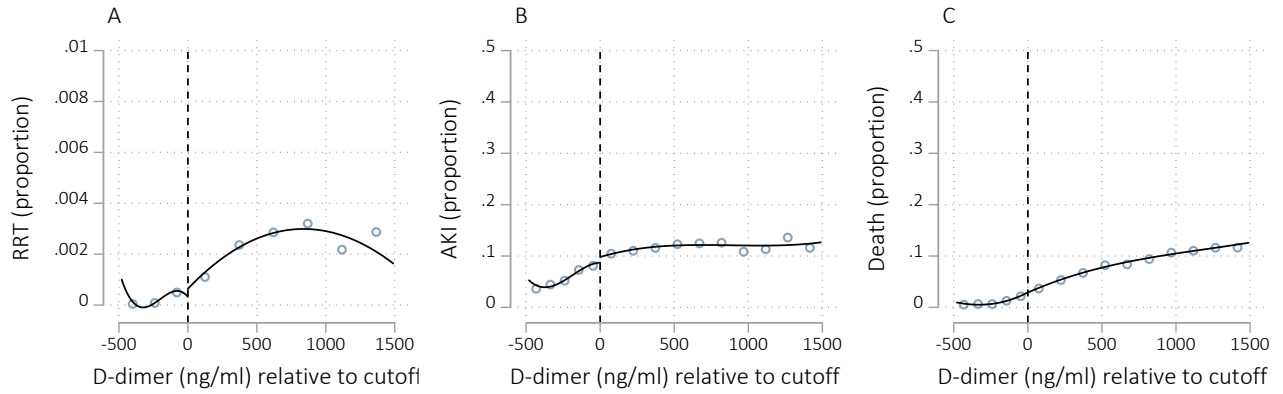
eFigure 3
Missingness (A) and timing (B) of data collection for primary outcome, long-term eGFR
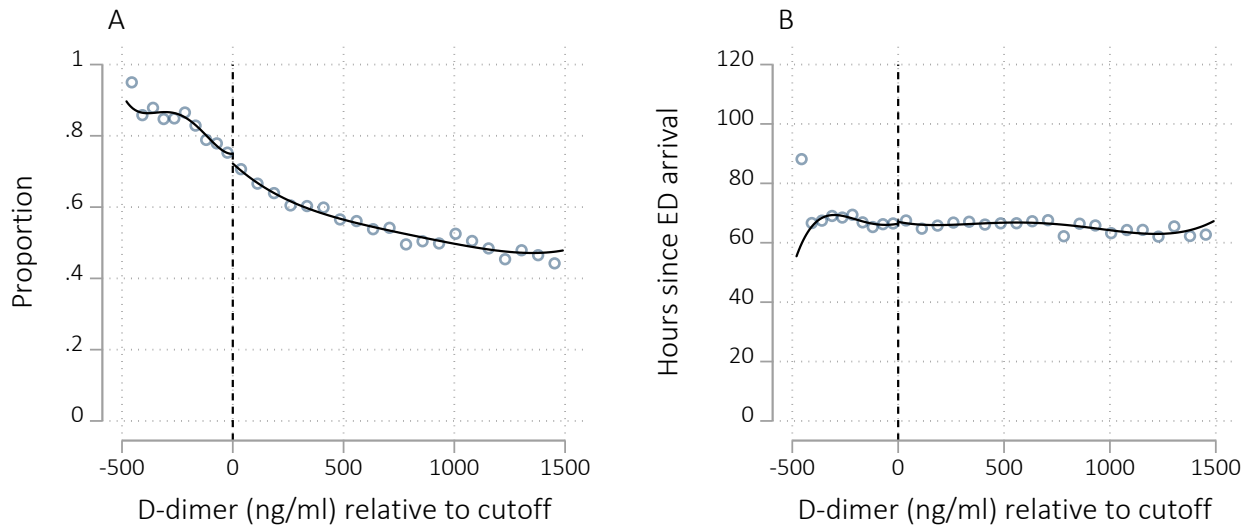
A

B
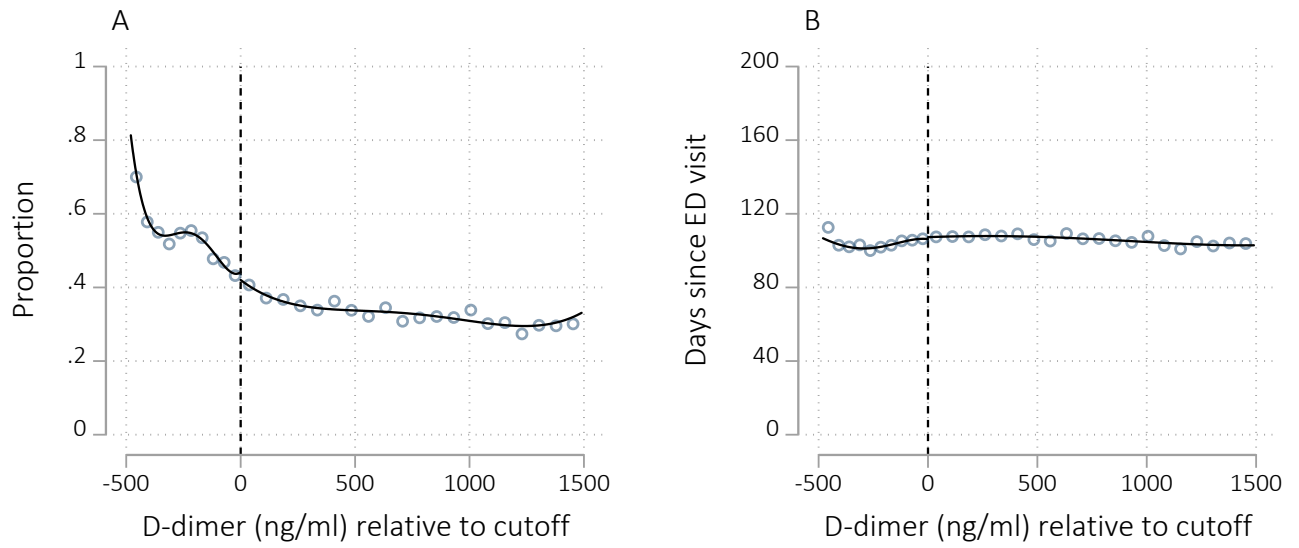
eFigure 4
Association between running variable, D-dimer, and need for renal replacement therapy within 6 months (A), acute kidney injury within 7 days (B), and call-cause mortality (C)
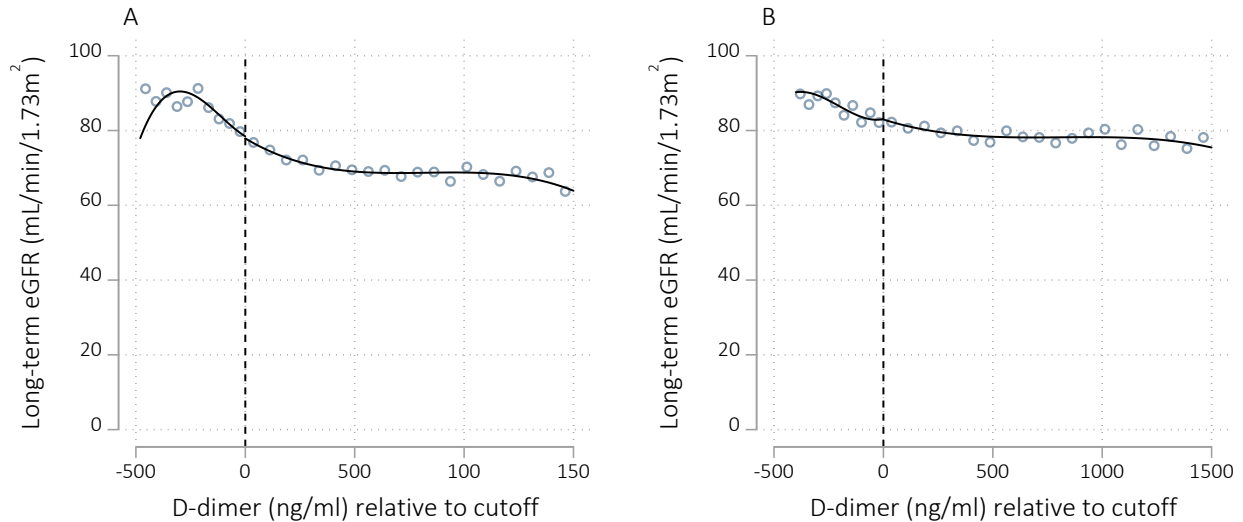

eFigure 5
Missingness (A) and timing (B) of data collection for acute kidney injury outcome

eFigure 6

Association between running variable, D-dimer, and long-term eGFR among those unexposed to CTPA (A) and those exposed to CTPA (B)

In A (CTPA unexposed), subjects below the cutoff are a mix of compliers (people whose CTPA receipt is determined by the cutoff) and non-complier 'never-takers' (people who *would* not have received a CTPA even if their D-dimer value was above the cutoff); subjects above the cutoff are all non-complier 'never-takers'. In B (CTPA exposed), subjects below the cutoff are all non-complier 'always-takers' (people who received a CTPA despite being below the cutoff); subjects above the cutoff are a mix of compliers and non-complier 'always-takers' (people who *would* have still received a CTPA even if their value was below the cutoff). A lack of outcome discontinuity at the cutoff is consistent with no significant difference between compliers, for whom our fuzzy RDD effect is estimated, and non-compliers.

References

1. Bertanha M, Imbens GW. External Validity in Fuzzy Regression Discontinuity Designs. *Journal of Business & Economic Statistics*. 2020;38(3):593-612. doi:10.1080/07350015.2018.1546590

2. Calonico S, Cattaneo MD, Farrell MH, Titiunik R. Rdrobust: Software for Regression-discontinuity Designs: *The Stata Journal*. Published online June 1, 2017. doi:10.1177/1536867X1701700208