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Original Investigation

High-Risk Clinical Presentations in Atherosclerotic Renovascular Disease: Prognosis and Response to Renal Artery Revascularization

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Background: Current trial data may not be directly applicable to patients with the highest risk presentations of atherosclerotic renovascular disease, including flash pulmonary edema, rapidly declining kidney function, and refractory hypertension. We consider the prognostic implications of these presentations and response to percutaneous revascularization.

Study Design: Single-center prospective cohort study; retrospectively analyzed.

Setting & Participants: 467 patients with renal artery stenosis ≥50%, managed according to clinical presentation and physician/patient preference.

Predictors: Presentation with flash pulmonary edema (n = 37 [7.8%]), refractory hypertension (n = 116 [24.3%]), or rapidly declining kidney function (n = 46 [9.7%]) compared to low-risk presentation with none of these phenotypes (n = 230 [49%]). Percutaneous revascularization (performed in 32% of flash pulmonary edema, 28% of rapidly declining kidney function, and 28% of refractory hypertension patients) compared to medical management.

Outcomes: Death, cardiovascular (CV) event, end-stage kidney disease.

Results: During a median follow-up of 3.8 (IQR, 1.8-5.8) years, 55% died, 33% had a CV event, and 18% reached end-stage kidney disease. In medically treated patients, flash pulmonary edema was associated with increased risk of death (HR, 2.2; 95% CI, 1.4-3.5; $P < 0.001$) and CV event (HR, 3.1; 95% CI, 1.7-5.5; $P < 0.001$), but not end-stage kidney disease, compared to the low-risk phenotype. No increased risk for any end point was observed in patients presenting with rapidly declining kidney function or refractory hypertension. Compared to medical treatment, revascularization was associated with reduced risk for death (HR, 0.4; 95% CI, 0.2-0.9; $P = 0.01$), but not CV event or end-stage kidney disease, in patients presenting with flash pulmonary edema. Revascularization was not associated significantly with reduced risk for any end point in rapidly declining kidney function or refractory hypertension. When these presentations were present in combination (n = 31), revascularization was associated with reduced risk for death (HR, 0.15; 95% CI, 0.02-0.9; $P = 0.04$) and CV event (HR, 0.23; 95% CI, 0.1-0.6; $P = 0.02$).

Limitations: Observational study; retrospective analysis; potential treatment bias.

Conclusions: This analysis supports guidelines citing flash pulmonary edema as an indication for renal artery revascularization in atherosclerotic renovascular disease. Patients presenting with a combination of rapidly declining kidney function and refractory hypertension also may benefit from revascularization and may represent a subgroup worthy of further investigation in more robust trials.

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INDEX WORDS: Atherosclerotic renovascular disease; renal artery stenosis; flash pulmonary edema; resistant hypertension; rapid loss of kidney function; renal revascularization.

Editorial, p. 175

Atherosclerotic renovascular disease (ARVD) affects significant numbers of patients and is associated with increased morbidity and mortality.[1] Until publication of the ASTRAL (Angioplasty and Stent for Renal Artery Lesions) trial results in 2009,[2] a total of 16% of incident patients with ARVD in the United States underwent renal artery revascularization[3] despite a lack of clear evidence for benefit and with some risk of complications.[4] The ASTRAL trial demonstrated that for patients with ARVD and largely stable chronic kidney disease (CKD), revascularization did not offer overall benefits versus medical therapy, a finding mirrored in clinical practice.[5] There has been a subsequent decrease in the number of renal revascularization procedures, with United Kingdom hospital episode statistics showing a 70% reduction between 2006 and 2010.[6]

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A limitation that reduced the generalizability of the ASTRAL trial's findings is that it included a higher proportion of stable and lower risk patients than might be typical of those referred for revascularization in clinical practice. Despite limited evidence supporting the practice, patients historically have undergone revascularization to treat flash pulmonary edema, refractory hypertension, and rapidly declining kidney function, with published guidelines endorsing this approach.[7] Clinical consensus and physician preference resulted in many of these patients undergoing revascularization outside of the ASTRAL trial and thus excluded from analysis. For example, at the highest recruiting center for the ASTRAL trial, there were 283 patients eligible for randomization during the period of the trial, and of these, 71 (25%) underwent randomization, with 24 (8.5%) undergoing revascularization outside of the study. It is likely that these were patients considered to have a definite clinical indication for intervention. As ASTRAL and other smaller randomized controlled trials have effectively ended the practice of revascularization for renal artery stenosis in clinically stable patients, it reasonably can be assumed that most revascularization procedures performed outside a trial setting are now for one of the aforementioned indications. However, although for each presentation there are case reports describing improved clinical status following revascularization,[8-11] none of these clinical subgroups has been studied robustly in a controlled trial, and no study has included a medically treated control group or assessed major clinical end points such as death. Until such data are available, interrogation of high-quality nonrandomized cohort data can provide important guidance.

This study aims to consider the following: (1) whether presentation with flash pulmonary edema, refractory hypertension, or rapidly declining kidney function is associated with an increased risk of death, cardiovascular (CV) event, or progression to end-stage kidney disease compared to presentation without these phenotypes; (2) the effect of revascularization compared to medical treatment for each high-risk presentation; and (3) whether the effect of revascularization compared to medical treatment differs in patients with 2 or more high-risk presentations.

METHODS

Description of Cohort and Inclusion Criteria

Since 1995, information about all patients referred to our tertiary renal center (catchment population, 1.55 million) diagnosed with ARVD (either by intra-arterial digital subtraction angiography or computed tomography/magnetic resonance angiography) has been entered into a prospectively populated database. Each patient record is updated annually by nephrology residents and contains details of imaging results, clinical presentation, comorbid conditions, CV events, prescribed medications, blood pressure, and laboratory measurements (estimated glomerular filtration rate [eGFR] calculated using the CKD-EPI [CKD Epidemiology Collaboration] creatinine equation[12]). Baseline details are defined at the time of diagnostic imaging.

Inclusion criteria for this analysis were complete baseline data and a minimum 50% unilateral renal artery stenosis on biplane measurement. Patients with a unilateral occlusion and insignificant contralateral stenosis were excluded, as this pattern of disease was thought unlikely to benefit from percutaneous revascularization. Approval was granted by the regional ethics committee.

Management

All patients were managed in accordance with published guidelines for vascular protective therapies and UK Renal Association blood pressure targets.[13] Patients underwent revascularization either due to prevailing beliefs of managing clinicians or

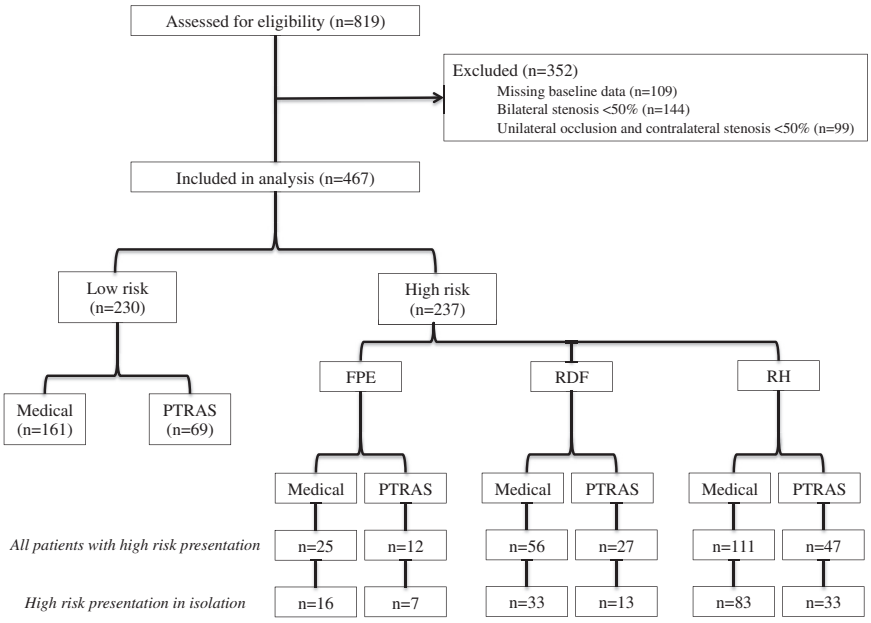

Figure 1. Patient selection and distribution. Abbreviations: FPE, flash pulmonary edema; PTRAS, percutaneous transluminal renal angioplasty with (bare metal) stenting; RDF, rapidly declining kidney function; RH, refractory hypertension.

Table 1. Baseline Patient Characteristics *(continued on following page)*

	All Patients (N = 467)			Low-Risk Patients (n = 237)			Flash Pulmonary Edema (n = 37)		
	Medical (n = 340)	PTRAS (n = 127)	*P*	Medical (n = 179)	PTRAS (n = 58)	*P*	Medical (n = 25)	PTRAS (n = 12)	*P*
Age (y)	71 ± 9	67.9 ± 8.9	<0.001	70.3 ± 9.7	67.3 ± 8.6	0.04	72.4 ± 4.2	62.7 ± 6.7	<0.001
eGFR (mL/min/1.73 m^2)	35 ± 20	36.6 ± 20.5	0.5	35.7 ± 21.5	40.1 ± 22.3	0.2	29.6 ± 21.2	34.3 ± 16.5	0.5
24-h urinary protein (g/24 h)	0.8 ± 1.1	0.8 ± 0.8	0.8	0.9 ± 1.4	1 ± 0.9	0.7	0.9 ± 0.8	0.7 ± 0.5	0.4
Systolic BP (mm Hg)	154.5 ± 29.6	162.5 ± 29.8	0.01	151 ± 32.3	155.5 ± 32.3	0.4	149.7 ± 30	172 ± 21.4	0.03
Diastolic BP (mm Hg)	79.2 ± 16.6	83.2 ± 16.3	0.03	79.8 ± 17.5	82.3 ± 17.7	0.4	75.8 ± 19.2	83.2 ± 12.4	0.3
No. of antihypertensive agents	2.5 ± 1.3	2.8 ± 1.4	0.1	2 ± 1	2.1 ± 0.9	0.3	2.7 ± 1.3	2.7 ± 1.7	0.9
Total cholesterol (mg/dL)	174 ± 46	182 ± 46	0.2	174 ± 46	174 ± 39	0.8	158 ± 35	197 ± 66	0.09
Left stenosis (%)	53.1 ± 32.3	61.5 ± 30.6	0.01	53.1 ± 31.9	60.3 ± 29.6	0.1	57.2 ± 33.6	58.8 ± 33.3	0.9
Right stenosis (%)	51.3 ± 31.8	60 ± 34	0.01	53.8 ± 31.1	57.3 ± 37.1	0.5	54.4 ± 36.3	57.9 ± 38.2	0.8
Patency score	95.6 ± 44	78.5 ± 44.9	<0.001	93.1 ± 45.2	82.3 ± 48.1	0.1	88.4 ± 49.3	83.3 ± 49.6	0.8
Angina	114 (33.6%)	50 (39.4%)	0.3	58 (32.6%)	20 (34.5%)	0.8	12 (48%)	5 (41.7%)	0.7
Myocardial infarction	101 (29.7%)	49 (38.6%)	0.07	57 (31.8%)	24 (41.4%)	0.2	8 (32%)	4 (33.3%)	0.9
Stoke/TIA	128 (37.6%)	54 (42.5%)	0.3	61 (34.1%)	22 (37.9%)	0.6	12 (48%)	6 (50%)	0.9
PVD	129 (37.9%)	55 (43.3%)	0.3	72 (40.2%)	30 (51.7%)	0.1	8 (32%)	3 (25%)	0.6
Diabetes	112 (32.9%)	39 (30.7%)	0.7	58 (32.4%)	14 (24.1%)	0.2	6 (24%)	4 (33.3%)	0.6
Current smoking	60 (17.6%)	23 (18.1%)	0.9	29 (16.2%)	9 (15.5%)	0.9	7 (28%)	4 (33.3%)	0.7
Angiotensin blockade	162 (47.6%)	66 (52%)	0.4	70 (39.1%)	30 (51.7%)	0.09	11 (44%)	2 (16.7%)	0.1
Aspirin	178 (53.1%)	77 (61.1%)	0.1	89 (50.9%)	33 (57.9%)	0.4	16 (66.7%)	5 (41.7%)	0.2
Statin	189 (56.4%)	69 (54.8%)	0.8	81 (46.3%)	29 (50.9%)	0.6	12 (50%)	4 (33.3%)	0.3

Note: Values for categorical variables are given as number (percentage); values for continuous variables, as mean ± standard deviation. Patient groups for individual presentations are mutually exclusive. Patients with rapid loss of kidney function and refractory HTN have a single disease presentation and do not feature in any other group. The flash pulmonary edema group contains patients with flash pulmonary edema as a lone presentation and patients with flash pulmonary edema in combination with either refractory HTN or rapid loss of kidney function; none of these patients are represented in other groups. Patients in the low-risk group are those without flash pulmonary edema, refractory HTN, or rapid loss of kidney function and represent a single category of patients. Conversion factor for cholesterol in mg/dL to mmol/L, ×0.02586. *(continued on following page)*

after entry into a randomized trial (ASTRAL, n = 35; CORAL [Cardiovascular Outcomes in Renal Atherosclerotic Lesions], n = 2) rather than because of a definitive departmental protocol. All renal revascularization procedures were performed in accordance with standard protocols for angioplasty coupled with bare-metal stent placement and standard antiplatelet therapy. Embolic protection devices were not deployed; no surgical bypass procedures were performed.

Definition of Exposures

High-risk presentations were identified by retrospective review of the database and medical notes by 2 independent observers. When disparity of opinion existed, cases were discussed to reach consensus.

Flash pulmonary edema was defined clinically. All patients with at least one episode of rapid-onset acute decompensated heart failure[14] were considered and medical records and echocardiographic data were reviewed. When there was evidence of an alternative cause (eg, acute myocardial infarction or arrhythmia) or documented chronic congestive cardiac failure/left ventricular ejection fraction <40%, patients were not defined as having flash pulmonary edema.

Refractory hypertension was defined in accordance with European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines as blood pressure above target (>140 mm Hg systolic and/or >90 mm Hg diastolic) despite use of 3 or more different classes of antihypertensive agents (including a diuretic).[15]

Rapidly declining kidney function was defined, as in ASTRAL, as serum creatinine level at angiography more than 1.2-fold or 1.14 mg/dL (100 μmol/L) greater than a baseline reading within the previous 6 months.

Patients with none of the mentioned presentations were classified as low risk.

Follow-up, Definition, and Ascertainment of Outcomes

Time zero was defined as the date of diagnostic angiography. Censoring occurred at the earliest of July 31, 2011; death; or last patient encounter. Predefined study end points were as follows: (1) death, including date and, when available, cause of death; (2) first

Table 1 (Cont'd). Baseline Patient Characteristics

Rapidly Declining Kidney Function (n = 46)			Refractory HTN (n = 116)			Rapidly Declining Kidney Function & Refractory HTN (n = 31)		
Medical (n = 33)	PTRAS (n = 13)	*P*	Medical (n = 83)	PTRAS (n = 33)	*P*	Medical (n = 20)	PTRAS (n = 11)	*P*
74.2 ± 6.1	72.4 ± 3.6	0.3	70.5 ± 9.7	68 ± 10.8	0.2	72.1 ± 7.8	71 ± 7	0.7
29.4 ± 13.4	29.3 ± 15.2	0.9	38.4 ± 19.4	34.7 ± 19.8	0.4	30.8 ± 12	34.8 ± 21.6	0.5
0.7 ± 0.6	0.5 ± 0.5	0.4	0.8 ± 0.9	0.7 ± 0.6	0.8	0.8 ± 0.8	0.7 ± 0.5	0.7
146.5 ± 27.4	141.2 ± 23.5	0.5	164.9 ± 24	174.9 ± 24.8	0.06	160.6 ± 17	176.5 ± 21.2	0.03
76.6 ± 16.1	74.7 ± 8.8	0.7	79.1 ± 14.3	87 ± 17.5	0.01	82.6 ± 16.1	85.9 ± 13.5	0.6
2.2 ± 1.4	2.4 ± 0.7	0.7	3.6 ± 1.1	3.5 ± 1.5	0.9	3.6 ± 1	4.2 ± 1.1	0.1
170 ± 42	159 ± 35	0.3	174 ± 46	201 ± 43	0.01	174 ± 46	166 ± 50	0.7
49.4 ± 32.2	59.6 ± 32.2	0.3	53.4 ± 32.6	65 ± 31.6	0.08	52.8 ± 35.7	62.3 ± 33	0.5
47.9 ± 28.8	52.3 ± 23.1	0.6	43.6 ± 34	65.1 ± 32.6	<0.001	62.3 ± 21.4	70 ± 28	0.4
102.7 ± 37.1	88.1 ± 32.4	0.2	103 ± 41.9	69.9 ± 41.3	<0.001	85 ± 42.6	67.7 ± 46.8	0.3
14 (42.4%)	8 (61.5%)	0.2	24 (28.9%)	13 (39.4%)	0.3	6 (30%)	4 (36.4%)	0.7
12 (36.4%)	7 (53.8%)	0.3	20 (24.1%)	11 (33.3%)	0.3	4 (20%)	3 (27.3%)	0.6
12 (36.4%)	5 (38.5%)	0.9	29 (34.9%)	18 (54.5%)	0.05	14 (70%)	3 (27.3%)	0.02
8 (24.2%)	6 (46.2%)	0.2	36 (43.4%)	13 (39.4%)	0.7	5 (25%)	3 (27.3%)	0.9
14 (42.4%)	6 (46.2%)	0.8	28 (33.7%)	8 (24.2%)	0.3	6 (30%)	7 (63.6%)	0.07
5 (15.2%)	2 (15.4%)	0.9	17 (20.5%)	6 (18.2%)	0.8	2 (10%)	2 (18.2%)	0.5
17 (51.5%)	6 (46.2%)	0.7	51 (61.4%)	19 (57.6%)	0.7	13 (65%)	9 (81.8%)	0.3
9 (27.3%)	11 (84.6%)	<0.001	54 (65.1%)	21 (63.6%)	0.9	10 (50%)	7 (63.6%)	0.5
22 (66.7%)	11 (84.6%)	0.2	58 (69.9%)	14 (42.4%)	0.01	16 (80%)	11 (100%)	0.1

Abbreviations and definitions: BP, blood pressure; eGFR, estimated glomerular filtration rate calculated by Chronic Kidney Disease Epidemiology Collaboration creatinine equation; HTN, hypertension; Medical, medically treated; PTRAS, percutaneous transluminal renal angioplasty with (bare metal) stenting; PVD, peripheral vascular disease; TIA, transient ischemic attack.

documented CV event, defined as myocardial infarction/acute coronary syndrome; hospitalization for pulmonary edema or arrhythmia; stroke, or transient ischemic attack; or new onset of symptomatic angina or deterioration of existing angina requiring interventional procedure; the date of index event or diagnostic procedure was recorded; and (3) end-stage kidney disease, defined as the earliest documented occurrence of long-term dialysis therapy initiation, kidney transplantation, or eGFR < 10 mL/min/1.73 m^2 (the level below which dialysis therapy typically is initiated in the United Kingdom).

Statistical Analysis

Normally distributed values are presented as mean ± standard deviation, whereas non–normally distributed data are presented as median (interquartile range [IQR]). Baseline continuous variables were compared using analysis of variance methods appropriate to distribution of data, with categorical variables compared using χ^2 test.

Survival analysis was performed using Cox proportional hazards weighted by inverse probability of treatment assignment.[16] Probability of treatment was calculated by logistic regression using clinically relevant variables with $\alpha < 0.1$ in univariate analysis. Age, eGFR, proteinuria, blood pressure, and burden of stenosis were entered into the model (Table S1, available as online supplementary material). Because most patients had a degree of bilateral disease, a patency score was calculated, with a score of 200 representing 0% bilateral stenosis and a score of 0 representing 100% bilateral stenosis.[17] Cox models were adjusted for the presence of diabetes mellitus and baseline use of angiotensin blockade when appropriate. Individual models were constructed for each disease presentation. Unadjusted event rates were calculated manually, with relative rates calculated using Poisson regression adjusted for the mentioned covariates. Predicted time to death for different values of continuous baseline variables were assessed graphically by negative binomial regression.

Time-averaged rate of change in kidney function was calculated using an unconditional linear growth model (unstructured covariance matrix) to allow for variation in eGFR within subjects. Differences in annual blood pressure records were compared between groups using repeated-measures analysis of variance. Statistical significance was defined as $\alpha < 0.05$.

Analyses were performed to compare the effect of putative high-risk presentations on outcome (using low-risk patients as reference group), and the effect of revascularization versus medical therapy within each high-risk group. Hence, the first comparisons were between patients with an individual high-risk presentation and low-risk patients (eg, patients with refractory hypertension as an

Table 2. Summary of Events Divided by Clinical Presentation *(continued on following page)*

	All Patients			Low Risk			Flash Pulmonary Edema		
	All (N = 467)	Medical (n = 340)	PTRAS (n = 127)	All (n = 237)	Medical (n = 179)	PTRAS (n = 58)	All (n = 37)	Medical (n = 12)	PTRAS (n = 25)
Death	255 (55%)	189 (56%)	66 (52%)	135 (57%)	104 (58%)	31 (53%)	26 (50%)	19 (76%)	7 (58%)
CV event[a]	155 (33%)	110 (32%)	45 (35%)	71 (30%)	54 (30%)	17 (29%)	17 (46%)	12 (48%)	5 (41%)
ESKD[b]	83 (18%)	60 (18%)	23 (18%)	43 (18%)	32 (18%)	11 (19%)	9 (24%)	6 (24%)	3 (25%)

Note: Values are given as number (percentage).

Abbreviations: CV, cardiovascular; ESKD, end-stage kidney disease; HTN, hypertension; Medical, medically treated; PTRAS, percutaneous transluminal renal angioplasty with (bare metal) stenting. *(continued on following page)*

isolated presentation vs patients with no high-risk presentation). The second comparison was between treatments within each presentation (eg, patients who underwent revascularization with refractory hypertension vs medically treated patients with refractory hypertension). Refractory hypertension and rapid loss of kidney function were considered in isolation. Due to limited patient numbers, all patients with flash pulmonary edema were considered (ie, including those with flash pulmonary edema and another high-risk presentation).

All analyses were performed using SAS, version 9.2 (SAS Institute Inc), licensed to the University of Manchester.

RESULTS

A total of 819 patient records were reviewed, with 109 excluded due to incomplete baseline data, 144 excluded due to renal artery stenosis <50%, and 99 excluded due to unilateral occlusion with stenosis <50% on the contralateral side. Data from 467 patients were analyzed, with a median follow-up of 3.8 (IQR, 1.8-5.8) years. Baseline demographics of excluded patients are presented in Table S2.

One or more high-risk presentation was exhibited by 237 (51%) patients, 58 (24%) of whom underwent revascularization; 230 (49%) patients were classified as low risk, with 69 (30%) of these undergoing revascularization. Overall, 37 patients had flash pulmonary edema (12 [32%] underwent revascularization), 83 had rapidly declining kidney function (27 [33%] underwent revascularization), and 158 had refractory hypertension (47 [30%] underwent revascularization). The patients presenting in only one high-risk group were as follows: flash pulmonary edema, 23 (7 [30%] underwent revascularization); rapidly declining kidney function, 46 (13 [28%] underwent revascularization); and refractory hypertension, 116 (33 [28%] underwent revascularization). Multiple high-risk presentations were identified in 45 patients (42 having 2 presentations, 3 having all 3). Of these patients, 16 (36%) underwent revascularization. Patient selection and distribution are described in Fig 1.

Across the entire cohort, patients who underwent revascularization were significantly younger than medically treated patients (68 vs 71 years), with lower patency scores (79 vs 96) and higher blood pressures (163/83 vs 155/79 mm Hg). Comorbid conditions were evenly matched, with the exception of a higher rate of previous myocardial infarction in the revascularization group (39% vs 30%). For each individual high-risk presentation, patient characteristics were evenly matched, although patients who underwent revascularization were younger in the flash pulmonary edema group and had lower patency scores in the

Table 3. Associations Between High-Risk Presentations and Risk for End Point in Medically Managed Patients

	Flash Pulmonary Edema		Rapidly Declining Kidney Function		Refractory HTN	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Death	2.19 (1.39-3.47)	<0.001	0.69 (0.42-1.12)	0.1	0.82 (0.59-1.14)	0.2
CV event[a]	3.07 (1.71-5.51)	<0.001	0.77 (0.41-1.48)	0.4	1.10 (0.67-1.62)	0.9
ESKD[b]	1.89 (0.81-4.43)	0.1	0.72 (0.381-1.69)	0.5	0.82 (0.45-1.51)	0.5

Abbreviations: CI, confidence interval; CV, cardiovascular; ESKD, end-stage kidney disease; HR, hazard ratio; HTN, hypertension.

[a]CV event defined as myocardial infarction/acute coronary syndrome, hospitalization for pulmonary edema or arrhythmia, stroke or transient ischemic attack, new onset of symptomatic angina, or deterioration of existing angina requiring interventional procedure.

[b]ESKD defined as initiation of long-term renal replacement therapy, kidney transplantation, or estimated glomerular filtration rate < 10 mL/min/1.73 m^2.

Table 2 (Cont'd). Summary of Events Divided by Clinical Presentation

Rapidly Declining Kidney Function			Refractory HTN			Rapidly Declining Kidney Function & Refractory HTN		
All (n = 46)	Medical (n = 33)	PTRAS (n = 13)	All (n = 116)	Medical (n = 83)	PTRAS (n = 33)	All (n = 31)	Medical (n = 20)	PTRAS (n = 11)
21 (46%)	15 (45%)	6 (46%)	59 (51%)	38 (46%)	21 (63%)	14 (45%)	13 (65%)	1 (9%)
14 (30%)	9 (28%)	5 (38%)	38 (33%)	23 (28%)	15 (45%)	15 (48%)	12 (60%)	3 (27%)
7 (15%)	5 (15%)	2 (15%)	17 (15%)	11 (13%)	6 (18%)	7 (23%)	6 (30%)	1 (9%)

[a]CV event defined as myocardial infarction/acute coronary syndrome, hospitalization for pulmonary edema or arrhythmia, stroke or transient ischemic attack, new onset of symptomatic angina, or deterioration of existing angina requiring interventional procedure.
[b]ESKD defined as initiation of long-term renal replacement therapy, kidney transplantation, or estimated glomerular filtration rate <10 mL/min/1.73 m^2.

refractory hypertension group. Complete baseline data are presented in Table 1, with summary outcome data presented in Table 2.

Medically treated patients with flash pulmonary edema had an increased hazard ratio (HR) for death and CV events compared with low-risk medically treated patients (HRs of 2.2 [95% confidence interval (CI), 1.4-3.5] and 3.1 [95% CI, 1.7-5.5], respectively; $P < 0.001$ for both), but not for end-stage kidney disease (HR, 1.9 [95% CI, 0.8-4.4]; $P = 0.1$). No significantly increased risk for any end point was observed in patients with rapidly declining kidney function or refractory hypertension (Table 3).

In the entire cohort, 127 (27%) patients underwent revascularization with a 93% documented technical success rate and 4.8% major complication rate. Median time from diagnosis to revascularization was 5.1 (IQR, 2.7-10.4) months. The effects of revascularization were analyzed on an intention-to-treat basis. When low-risk patients were considered alone, revascularization was not associated with a significant change in HRs for any major end point (HRs of 0.8 [95% CI, 0.7-1.2], 1.0 [95% CI, 0.8-1.2], and 1.0 [95% CI, 0.7-1.4] for death, CV events, and end-stage kidney disease, respectively).

In patients with flash pulmonary edema, revascularization was associated with a significant reduction in risk for death (HR, 0.43; 95% CI, 0.2-0.9; $P = 0.01$; Fig 2) with a corresponding reduction in event rate (deaths/100 patient-years: revascularization, 14; medical treatment, 37; $P = 0.02$). This survival benefit was observed across all levels of baseline eGFR (Fig S1). No reduction in HR for CV event or end-stage kidney disease was observed in patients who underwent revascularization with flash pulmonary edema (HRs of 1.1 [95% CI, 0.4-3.0] and 1.4 [95% CI, 0.4-5.2], respectively; $P >$ 0.7 for both); non–statistically significantly lower

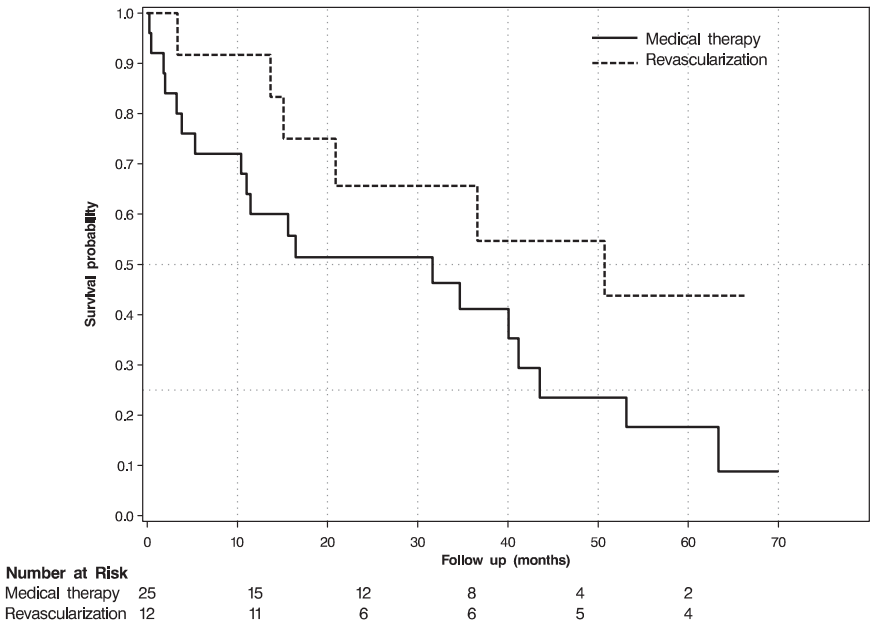

Figure 2. Kaplan-Meier survival plot for patients presenting with flash pulmonary edema. Horizontal axis, time in months from diagnostic angiography; vertical axis, event-free survival; solid line, medically treated patients; dashed line, patients treated with percutaneous renal angioplasty with bare-metal stenting.

Table 4. Effect of Revascularization on Risk for and Rate of End Points Divided by Clinical Presentation *(continued on following page)*

	Flash Pulmonary Edema					Rapidly Declining Kidney Function				
	HR (95% CI)	*P*	Event Rate[a] (95% CI)	Relative Rate (95% CI)	*P*	HR (95% CI)	*P*	Event Rate[a] (95% CI)	Relative Rate (95% CI)	*P*
Death	0.43 (0.20-0.91)	0.01	37 (23-57) vs 14 (7-29)	0.36 (0.16-0.80)	0.02	0.80 (0.43-1.43)	0.5	11 (7-18) vs 10 (4-20)	0.91 (0.37-2.3)	0.9
CV event	1.13 (0.41-3.01)	0.8	31 (18-52) vs 14 (6-32)	0.44 (0.16-1.26)	0.2	1.76 (0.84-3.81)	0.2	9 (5-15) vs 12 (5-28)	1.54 (0.52-4.30)	0.4
ESKD	1.36 (0.35-5.2)	0.7	12 (5-27) vs 7 (2-22)	0.60 (0.15-2.41)	0.5	0.76 (0.36-2.17)	0.6	4 (2-10) vs 3 (1-14)	0.84 (0.18-4.1)	0.8

Note: Poisson model adjusted for age, kidney function, proteinuria, blood pressure, overall renal artery patency, sex, presence of diabetes, and use of angiotensin blockade. Results are presented as relative rate (95% CI). Cox model adjusted for presence of diabetes and use of angiotensin blockade when appropriate with weighting for inverse probability of treatment calculated from age, kidney function, blood pressure, proteinuria, and overall real artery patency score. Results are presented as hazard ratio (95% CI). *(continued on following page)*

CV event rates were seen in patients who underwent revascularization (revascularization, 14/100 patient-years; medical treatment, 32/100 patient-years; $P = 0.2$).

No difference in risk for death or end-stage kidney disease was observed in patients who underwent revascularization who presented with rapidly declining kidney function or refractory hypertension. However, non–statistically significant increases in risk for CV events were seen in patients who underwent revascularization in both these groups (HRs of 1.8 [95% CI, 0.8-3.8; $P = 0.2$] and 1.3 [95% CI, 0.8-1.9; $P = 0.3$] for rapidly declining kidney function and refractory hypertension, respectively). The same trend was observed when event rates were considered for these presentations (medical treatment vs revascularization): event rates of 9 versus 12/100 patient-years ($P = 0.4$) for rapidly declining kidney function and 9 versus 12/100 patient-years ($P = 0.3$) for refractory hypertension. Complete data are presented in Table 4.

Limited patient numbers precluded meaningful assessment of combined flash pulmonary edema and rapidly declining kidney function (8 patients, 3 underwent revascularization), or flash pulmonary edema and refractory hypertension (8 patients, 2 underwent revascularization). However, sufficient patients presented with refractory hypertension and rapid loss of kidney function (31 patients, 11 underwent revascularization) for analysis. In this patient group, medical treatment was associated with increased risks for CV events and end-stage kidney disease (HRs of 2.1 [95% CI, 1.2-3.8] and 2.4 [95% CI, 1.3-3.9], respectively; $P < 0.02$ for both), but not death (HR, 1.2 [95% CI, 0.8-2.0]; $P = 0.4$). Revascularization was associated with significant reductions in both risk for death (HR, 0.12 [95% CI, 0.02-0.77]; $P = 0.03$; Fig 3) and CV event (HR, 0.28 [95% CI, 0.10-0.60]; $P < 0.001$). There were insufficient end points (medical treatment group, 8; revascularization group, 1) to meaningfully comment on risk for progression to end-stage kidney disease (Table 4).

Within the entire cohort, the median rate of loss of kidney function was 2 mL/min/1.73 m^2 per year, with no significant difference between medically treated patients and those who underwent revascularization. No difference in rate of eGFR loss was observed between medically treated patients and those who underwent revascularization in any high-risk subgroup. Systolic and diastolic blood pressures decreased in both medically treated patients and those who underwent revascularization within each group. No significant differences in blood pressure reductions between the medically treated and revascularized groups were observed for any high-risk presentation, with the exception of a greater reduction in diastolic blood pressure in patients who underwent revascularization with refractory hypertension at baseline (Table 5).

DISCUSSION

To our knowledge, this cohort of 467 patients with an overall revascularization rate of 27%, comparable to that seen in Medicare claims data,[3] includes the largest series of patients with flash pulmonary edema, and the only series of patients with flash pulmonary edema to include a medically treated comparator group. These data, representing more than 15 years of clinical practice, reflect the findings of the ASTRAL trial and other randomized trials in a real-life setting: for an unselected population of patients with ARVD, revascularization does not alter any hard clinical outcome. This top-line finding is because low-risk patients do not benefit. With the most recent trials describing the potential for serious complications of revascularization,[2,18] acceptance of this is vital to prevent exposure of patients to unnecessary risks.

Table 4 (Cont'd). Effect of Revascularization on Risk for and Rate of End Points Divided by Clinical Presentation

Refractory HTN					Rapidly Declining Kidney Function & Refractory HTN				
HR (95% CI)	*P*	Event Rate[a] (95% CI)	Relative Rate (95% CI)	*P*	HR (95% CI)	*P*	Event Rate[a] (95% CI)	Relative Rate (95% CI)	*P*
1.09 (0.77-1.55)	0.6	12 (8-19) vs 12 (8-16)	1.05 (0.62-1.80)	0.8	0.15 (0.02-0.94)	0.04	18 (11-30) vs 2 (0.3-16)	0.14 (0.01-0.99)	0.01
1.30 (0.79-1.9)	0.3	9 (6-13) vs 12 (8-21)	1.43 (0.75-2.8)	0.3	0.28 (0.1-0.79)	0.02	19 (10-32) vs 8 (2-24)	0.4 (0.11-1.4)	0.1
1.25 (0.71-2.26)	0.3	4 (3-7) vs 4 (2-9)	1.10 (0.41-2.97)	0.8			Insufficient end-points		

Abbreviations: CI, confidence interval; CV, cardiovascular; ESKD, end-stage kidney disease; HR, hazard ratio; HTN, hypertension; PTRAS, percutaneous transluminal renal angioplasty with (bare metal) stenting.

[a]Event rate of medically treated versus PTRAS-treated patients, expressed per 100 patient-years.

However, this study emphasizes that a significant proportion of patients with ARVD (51% in this cohort) present in a manner that could be considered higher risk based on current guidance.

We have demonstrated that of these 3 putative high-risk presentations (flash pulmonary edema, rapidly declining kidney function, and refractory hypertension), only flash pulmonary edema can be considered to be an adverse prognostic marker, with significantly increased risks for death and CV events associated with this presentation in medically treated patients. As importantly, we have shown an association between revascularization and a reduced risk for death for this presentation. While Cox analysis did not demonstrate a reduction in risk for CV events in patients with flash pulmonary edema who underwent revascularization, a result in contrast to existing data,[8] there was a trend toward reduced event rates. We therefore would suggest that the apparent lack of benefit from revascularization in terms of CV events could be a function of improved survival in a high-risk patient group. Our findings provide support for current guidelines[7] citing flash pulmonary edema as an indication for revascularization. This is important because the guidelines are based largely on consensus opinion, because underpinning data have been derived predominantly from case series.[8,19,20] Previous reports have demonstrated that revascularization for flash pulmonary edema can significantly reduce the rate of hospitalization with decompensated heart failure.[8] Potentially, revascularization also may improve the structural cardiac changes seen in ARVD as described in case reports.[21,22] It remains to be seen whether cardiac imaging substudies of the ASTRAL trial will provide further pathophysiologic insights.[23]

No association with increased risk for any end point or any reduction in risk associated with revascularization was observed in patients presenting with

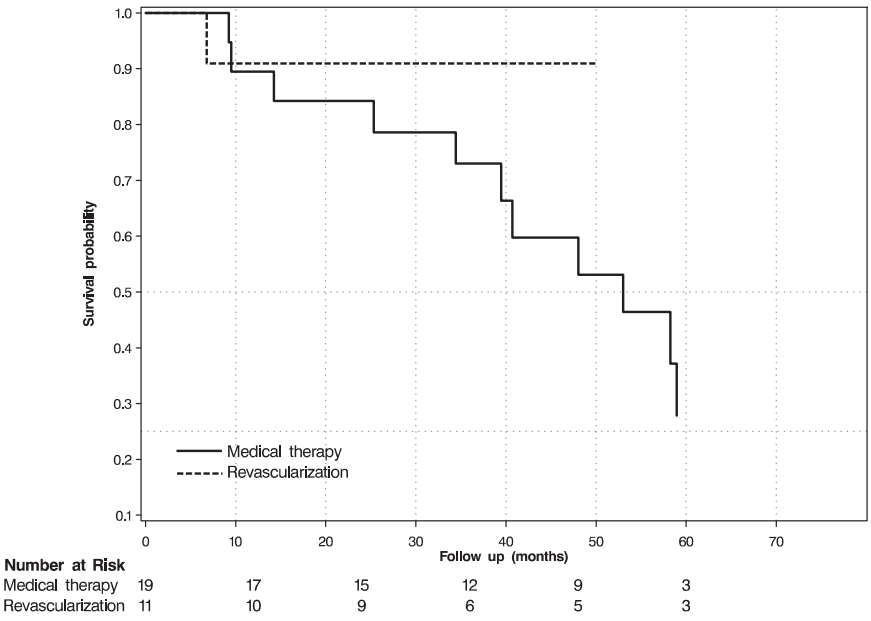

Figure 3. Kaplan-Meier survival plot for patients presenting with rapidly declining kidney function and refractory hypertension. Horizontal axis, time in months from diagnostic angiography; vertical axis, event-free survival; solid line, medically treated patients; dashed line, patients treated with percutaneous renal angioplasty with bare-metal stenting.

Table 5. Annual Differences in BP and Kidney Function Between Treatment Groups

	Treatment	Year 0	Year 1	Year 2	Year 3	*P* Within Group	*P* Between Groups
Flash Pulmonary Edema							
No. of patients with available data	Medical	25	16	12	9	—	—
	PTRAS	12	10	6	3	—	—
Systolic BP (mm Hg)	Medical	152 ± 31	137 ± 28	138 ± 34	132 ± 19	0.2	0.1
	PTRAS	171 ± 21	155 ± 17	142 ± 25	144 ± 21	0.05	
Diastolic BP (mm Hg)	Medical	78 ± 17	73 ± 13	73 ± 17	71 ± 8	0.4	0.2
	PTRAS	83 ± 12	81 ± 11	75 ± 8	86 ± 8	0.5	
Median annual eGFR change ($mL/min/1.73\,m^2$)	Medical		0.0 [−3.9 to +0.01]			—	0.3
	PTRAS		0.1 [−4.8 to +0.7]			—	
Rapidly Declining Kidney Function							
No. of patients with available data	Medical	33	29	25	18	—	—
	PTRAS	13	13	12	9	—	—
Systolic BP (mm Hg)	Medical	151 ± 28	144 ± 24	142 ± 25	147 ± 34	0.3	0.1
	PTRAS	139 ± 22	141 ± 33	131 ± 16	139 ± 23	0.8	
Diastolic BP (mm Hg)	Medical	79 ± 16	76 ± 15	75 ± 14	75 ± 15	0.4	0.02
	PTRAS	74 ± 9	69 ± 14	66 ± 11	63 ± 13	0.07	
Median annual eGFR change ($mL/min/1.73\,m^2$)	Medical		−0.38 [−3.1 to 0.0]			—	0.3
	PTRAS		−2.2 [−3.7 to 0.0]			—	
Refractory Hypertension							
No. of patients with available data	Medical	83	72	53	43	—	—
	PTRAS	33	29	24	20	—	—
Systolic BP (mm Hg)	Medical	166 ± 23	158 ± 25	152 ± 23	147 ± 24	<0.001	0.5
	PTRAS	175 ± 24	156 ± 29	148 ± 27	155 ± 21	<0.001	
Diastolic BP (mm Hg)	Medical	80 ± 14	78 ± 13	77 ± 13	73 ± 14	<0.001	0.3
	PTRAS	87 ± 17	80 ± 13	76 ± 12	79 ± 14	0.001	
Median annual eGFR change ($mL/min/1.73\,m^2$)	Medical		−2.6 [−5.8 to 0.1]			—	0.5
	PTRAS		−1.2 [−4.9 to 0.0]			—	
Rapidly Declining Kidney Function & Refractory Hypertension							
No. of patients with available data	Medical	20	18	16	13	—	—
	PTRAS	11	10	9	6	—	—
Systolic BP (mm Hg)	Medical	157 ± 19	157 ± 27	147 ± 24	157 ± 29	0.3	0.6
	PTRAS	177 ± 21	150 ± 17	146 ± 17	132 ± 27	0.001	
Diastolic BP (mm Hg)	Medical	81 ± 16	74 ± 12	73 ± 11	76 ± 9	0.03	0.8
	PTRAS	86 ± 13	70 ± 14	74 ± 13	70 ± 19	0.03	
Median annual eGFR change ($mL/min/1.73\,m^2$)	Medical		−3.2 [−11 to 0.5]			—	0.3
	PTRAS		−2.2 [−6.7 to 1.0]			—	

Note: Unless otherwise indicated, values are presented as mean ± standard deviation or median [interquartile range].

Abbreviations: BP, blood pressure; eGFR, estimated glomerular filtration rate; Medical, medically treated; PTRAS, percutaneous transluminal renal angioplasty with (bare metal) stenting.

rapidly declining kidney function or refractory hypertension. However, there was a suggestion that these phenotypes may be important when presenting in combination. Although patient numbers were small, significant reductions in risk for death and CV events were associated with revascularization in patients with both these phenotypes at baseline. This combination conceivably could be a clinical manifestation of a specific anatomical pattern amenable to revascularization (eg, high-grade anatomical stenosis with preserved renal parenchymal volume).[24] However, due to the range of diagnostic imaging methods and time frames during which data were acquired, estimation of renal volume could not be performed. Further study is required, but our findings would suggest that when the clinician is faced with a patient with ARVD with this combination, revascularization could be considered.

An important question raised by these results is whether either rapid loss of kidney function or refractory hypertension truly represents a high-risk clinical presentation of ARVD. We suggest that refractory hypertension by the definition used here does not. This may relate in part to the blunt nature

of clinic blood pressure as a marker of CV health with, for example, decreased left ventricular function, confounding by "masking" hypertension. Alternatively, this may reflect the fact that significantly elevated blood pressure is found in even low-risk patients with ARVD, or that successful treatment of hypertension can be achieved by pharmacologic methods in this patient group. Given the established effects of uncontrolled blood pressure in CKD,[25] it would be patently false to claim that no risk is associated with extreme values of blood pressure in patients with ARVD. However, our analysis suggests that there may be value in reconsidering where the threshold for increased risk lies in this patient group. The assessment of rapid loss of kidney function again is uncertain. Our data conflict with those from the subgroup analysis of patients with rapidly declining kidney function within the ASTRAL trial, in which patients who underwent revascularization showed a trend to reduced loss of kidney function at 12 months. In another study that compared medically treated patients from the United Kingdom with patients who underwent revascularization managed at a German center, a benefit in kidney function at 1 year was seen in patients with CKD stages 4-5 who underwent revascularization.[26] The disparity in outcomes may be explained by the longer follow-up in our study (ie, a nonsustained improvement in eGFR) or a difference in practice between countries in the twin-center study,[26] with ~50% of patients who underwent revascularization with rapidly declining kidney function in our cohort classified as CKD stage 3 at baseline. Patient-level analysis of existing randomized trials, examining different definitions of rapidly declining kidney function and refractory hypertension, may be of value.

Although the findings were nonsignificant, the trends toward increased CV risk in patients who underwent revascularization with rapid loss of kidney function and (to a lesser extent) refractory hypertension merit consideration. This may reflect unmeasured differences between treatment groups, which, although well matched for overall CV history at baseline, may have had important differences (eg, in burden of coronary atheroma).

In this study, the average rate of loss of kidney function across all groups was 2 mL/min/1.73 m^2 per year, only double that which might be accepted with aging,[27] a fact of importance for the design of future trials. This suggests limited utility in future studies considering progression to end-stage kidney disease as an end point. With an overall baseline eGFR of 33 mL/min/1.73 m^2 in this study (and similar values in published trials), prolonged follow-up would be required to observe difference in kidney function outcomes.

These analyses have been performed in a patient cohort in which detailed clinical and laboratory data have been prospectively and studiously collected over 15 years. Although the single-center patient management, rigor of data collection, and real-life setting are strengths of the work, there are still important limitations of what is a retrospective analysis: primarily a lack of patient randomization and the likelihood of selection bias. Although analyses were weighted for probability of receiving treatment, statistical techniques cannot account for unmeasured or intangible clinical factors, and uncontrolled confounding must be considered a possibility. Patient and event numbers limiting our ability to adjust within Cox models may have compounded this. Furthermore, it is inappropriate to claim that weighting by a selection of clinical measurements can completely reflect the complexity of making a treatment decision. That only 25% of potentially high-risk patients underwent revascularization may imply an unspecified selection bias (eg, with only the most unwell patients undergoing intervention), but this also may reflect the difficulty of the decision-making process based on currently available data and known risks of intervention. Although intervention at time of diagnostic angiography is performed by many centers, this has not been a standard practice at our center. Because our data set records only interventions that were undertaken as opposed to planned, it is possible that a small number of patients referred for revascularization may have died prior to receiving treatment. Because patients were analyzed by treatment received, this should be considered as a possible confounding issue. However, review of the notes of medically treated patients with flash pulmonary edema identified only one such patient who died waiting for revascularization. Interventional procedures for flash pulmonary edema also occurred over a shorter time frame (median time to revascularization, 1.6 [IQR, 0.3-5.9] months). Other relevant limitations of our study also should be highlighted. Stenosis grade was assessed in biplane measurement only (without measurement of renal resistive index or pressure gradient), and no information regarding rationale for investigation of ARVD was available (with variation in approach to diagnostic testing potentially influencing results). In addition, 32% of cases were diagnosed using magnetic resonance angiography, which may overestimate the degree of stenosis.[28] Medication type, but not dosage, is recorded, and the models used do not account for longitudinal changes in therapy or blood pressure. In addition clinical presentation was defined at the time of diagnostic angiography. Although local practice is to review the indication for intervention immediately prior to revascularization, we cannot account for any change in status between diagnosis and intervention. Finally, although our revascularization

rate is comparable to that in Medicare data, the rate of intervention for flash pulmonary edema is lower than might be anticipated, suggesting either treatment bias or a limitation of our definition. With 40% of patients with flash pulmonary edema in this series having bilateral stenosis ≥50%, we believe we successfully identified patients with a significant burden of renal arterial disease. As such, the lower than anticipated intervention rates may reflect the period over which these data have been recorded and the variation in access to revascularization services.

In summary, although this study has limitations, we believe that it provides strong data confirming flash pulmonary edema as a risk factor for adverse outcomes in ARVD and supporting revascularization for this presentation. The data regarding management of refractory hypertension and rapidly declining kidney function are less clear, in part due to imprecision of definition of the conditions and in part due to other confounders (eg, changes in medications), which were not available for analysis. Although medically treated patients with sole rapidly declining kidney function or refractory hypertension did not have increased risk for end points, the observed benefits from revascularization in the subgroup in which refractory hypertension and rapidly declining kidney function coexisted warrant further study to confirm the results and elucidate potential mechanisms.

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SUPPLEMENTARY MATERIAL

Table S1: Results of logistic regression for probability of revascularization.

Table S2: Comparison of included and excluded patients.

Figure S1: Predicted time to death by eGFR and treatment type in patients with flash pulmonary edema.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2013.07.020) is available at www.ajkd.org

REFERENCES

1. Kalra PA, Guo H, Gilbertson DT, et al. Atherosclerotic renovascular disease in the United States. *Kidney Int*. 2009;77(1):37-43.

2. ASTRAL Investigators; Wheatley K, Ives N, Gray R, et al. Revascularization versus medical therapy for renal-artery stenosis. *N Engl J Med*. 2009;361(20):1953-1962.

3. Kalra PA, Guo H, Kausz AT, et al. Atherosclerotic renovascular disease in United States patients aged 67 years or older: risk factors, revascularization, and prognosis. *Kidney Int*. 2005;68(1):293-301.

4. Leertouwer TC, Gussenhoven EJ, Bosch JL, et al. Stent placement for renal arterial stenosis: where do we stand? A meta-analysis. *Radiology*. 2000;216(1):78-85.

5. Valluri A, Severn A, Chakraverty S. Do patients undergoing renal revascularization outside of the ASTRAL trial show any benefit? Results of a single centre observational study. *Nephrol Dial Transplant*. 2012;27(2):734-738.

6. Health and Social Care Information Centre. United Kingdom Hospital Episode Statistics. http://www.hesonline.nhs.uk. Accessed December 12, 2011.

7. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA Guidelines for the Management of Patients with Peripheral Arterial Disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Associations for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (writing committee to develop guidelines for the management of patients with peripheral arterial disease)—summary of recommendations. *J Vasc Interv Radiol*. 2006;17(9):1383-1397.

8. Kane GC, Xu N, Mistrik E, Roubicek T, Stanson AW, Garovic VD. Renal artery revascularization improves heart failure control in patients with atherosclerotic renal artery stenosis. *Nephrol Dial Transplant*. 2010;25(3):813-820.

9. Kanamori H, Toma M, Fukatsu A. Improvement of renal function after opening occluded atherosclerotic renal arteries. *J Invasive Cardiol*. 2009;21(9):E171-E174.

10. Chrysochou C, Sinha S, Chalmers N, Kalra PR, Kalra PA. Anuric acute renal failure and pulmonary oedema: a case for urgent action. *Int J Cardiol*. 2009;132(1):e31-e33.

11. Kuznetsov E, Schifferdecker B, Jaber BL, Soukas P, Liangos O. Recovery of acute renal failure following bilateral renal artery angioplasty and stenting. *Clin Nephrol*. 2007;68(1):32-37.

12. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604-612.

13. Goddard J, Harris K, Turner N. The UK eCKD guide. http://www.renal.org. Accessed December 12, 2011.

14. Rimoldi SF, Yuzefpolskaya M, Allemann Y, Messerli F. Flash pulmonary edema. *Prog Cardiovasc Dis*. 2009;52(3):249-259.

15. Mancia G, De Backer G, Dominiczak A, et al. 2007 Guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J*. 2006;28(12):1462-1536.

16. Lunceford JKJ, Davidian MM. Stratification and weighting via the propensity score in estimation of causal treatment effects: a comparative study. *Stat Med*. 2004;23(19):2937-2960.

17. Suresh M, Laboi P, Mamtora H, Kalra PA. Relationship of renal dysfunction to proximal arterial disease severity in atherosclerotic renovascular disease. *Nephrol Dial Transplant*. 2000;15(5):631-636.

18. Bax L, Woittiez A-JJ, Kouwenberg HJ, et al. Stent placement in patients with atherosclerotic renal artery stenosis and impaired renal function: a randomized trial. *Ann Intern Med*. 2009;150(12):840-848.

19. Bloch MJ, Trost DW, Pickering TG, Sos TA, August P. Prevention of recurrent pulmonary edema in patients with bilateral renovascular disease through renal artery stent placement. *Am J Hypertens*. 1999;12(pt 1):1-7.

20. Gray BH, Olin JW, Childs MB, Sullivan TM, Bacharach JM. Clinical benefit of renal artery angioplasty with

stenting for the control of recurrent and refractory congestive heart failure. *Vasc Med*. 2002;7(4):275-279.

21. Wright JR, Shurrab AE, Cooper A, Kalra PR, Foley RN, Kalra PA. Left ventricular morphology and function in patients with atherosclerotic renovascular disease. *J Am Soc Nephrol*. 2005;16(9):2746-2753.

22. Chrysochou C, Sharma R, Kalra PA, Kalra PR. Improved left ventricular filling following bilateral renal artery stenting. *Int J Cardiol*. 2011;150(1):e40-e41.

23. Hegarty J, Wright JR, Kalra PR, Kalra PA. The heart in renovascular disease—an association demanding further investigation. *Int J Cardiol*. 2006;111(3):339-342.

24. Cheung CM, Chrysochou C, Shurrab AE, Buckley DL, Cowie A, Kalra PA. Effects of renal volume and single-kidney glomerular filtration rate on renal functional outcome in atherosclerotic renal artery stenosis. *Nephrol Dial Transplant*. 2010;25(4):1133-1140.

25. Klahr S, Levey AS, Beck GJ, et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. *N Engl J Med*. 1994;330(13):877-884.

26. Kalra PA, Chrysochou C, Green D, et al. The benefit of renal artery stenting in patients with atheromatous renovascular disease and advanced chronic kidney disease. *Cathet Cardiovasc Intervent*. 2010;75(1):1-10.

27. Hemmelgarn BR, Zhang J, Manns BJ, et al. Progression of kidney dysfunction in the community-dwelling elderly. *Kidney Int*. 2006;69(12):2155-2161.

28. Patel ST, Mills JL, Tynan-Cuisinier G, Goshima KR, Westerband A, Hughes JD. The limitations of magnetic resonance angiography in the diagnosis of renal artery stenosis: comparative analysis with conventional arteriography. *J Vasc Surg*. 2005;41(3):462-468.