to the lumen.[17] An array of engineered cell types could be created from induced pluripotent stem cells, each designed to deliver specific ions and solutes into the lumen of the colon or the urinary bladder. Quantitative considerations would determine the nature and size of such an organ.

MAJOR CHALLENGES AND OPPORTUNITIES

Important limitations of the above approaches are quantitative and would have to be matched by some degree of control of intake into the body. For instance, without the ability to concentrate or dilute the urine, control of volume intake matched to the level of ultrafiltration would be needed.

The major challenge, however, would be the bioengineering of the simplified filtration and secretory organs, something that is becoming increasingly feasible in the era of synthetic biology. Nonetheless, the currently more daunting and challenging task of designing a nephron, with its sequential processes of filtration, tubular absorption, and secretion, will be infinitely more difficult to achieve and an approach analogous to the "deconstructed" kidney model proposed herein may well be a more practical option.

DISCLOSURES

None.

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Persistent Underrepresentation of Kidney Disease in Randomized, Controlled Trials of Cardiovascular Disease in the Contemporary Era

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Over the last few decades, studies have consistently demonstrated an increased risk of ischemic heart disease, heart failure, and arrhythmias in patients with kidney disease (KD).[1] The presence of KD also confers significantly greater risk for poor outcomes in patients with cardiovascular disease (CVD).[2] But despite the established association between KD and CVD, randomized, controlled trials (RCTs) investigating CVD have historically excluded subjects with preexisting KD.[3–5]

To examine the representation of KD in CVD trials in the contemporary era, we performed a manual literature search of each individual issue of 22 major journals published in 2006 through 2014 to identify all RCTs targeting patients with chronic stable heart failure, acute myocardial infarction, atrial fibrillation, and stable coronary artery disease. The search strategy included articles from January 1, 2006 through December 31, 2014 with ≥100 trial participants. We excluded articles that were subgroup or *post hoc* analyses and trials that did not include mortality as a primary or secondary end point.

This group of 22 journals included four general medicine journals (Annals of Internal Medicine, Journal of the American Medical Association, The Lancet, and New England Journal of Medicine), five major CVD journals (American Heart Journal, Circulation, European Heart Journal, Journal of the American College of Cardiology [JACC], and Journal of the American Heart Association), three major nephrology journals (American Journal of Kidney Diseases, Journal of the American Society of Nephrology, and Kidney International), and ten CVD "daughter journals" (Circulation Arrhythmia and Electrophysiology, Circulation Cardiovascular Genetics, Circulation Cardiovascular Imaging, Circulation Cardiovascular Interventions, Circulation Cardiovascular Quality and Outcomes, Circulation Heart Failure, European Heart Journal Acute Cardiovascular Care, JACC Cardiovascular Imaging, JACC Cardiovascular Interventions, and JACC Heart Failure). The prior era pertains to the period from 1985 through 2005, in which underrepresentation of KD was examined by Coca *et al.*[5]

DATA FROM THE CONTEMPORARY VERSUS THE PRIOR ERA

Our analysis included 305 randomized trials with 696,935 participants. Contemporary RCTs (2006–2014) were significantly less likely than those in the prior era (1985–2005) to exclude people with KD (139 of 305 [46%] versus 86 of 153 [56%], $P=0.04$) (Table 1). Contemporary-era trials that had significantly lower rates of excluding patients with KD compared with older trials included multicenter studies (126 of 280 [45%] versus 83 of 138 [60%], $P<0.01$), trials enrolling ≥1000 patients (55 of 126 [44%] versus 57 of 90 [63%], $P<0.01$), North America–based trials (13 of 32 [41%] versus 48 of 64 [75%], $P<0.01$), and trials evaluating heart failure cohorts (29 of 57 [51%] versus 28 of 36 [78%], $P=0.02$).

The KD exclusion rates from the two eras did not differ on the basis of drug or device therapeutic class, primary funding source, or coronary artery disease status (Tables 1 and 2), nor did they differ over serial 5-year time periods from 1985 through 2014. However, the proportion of trials examining renin-angiotensin-aldosterone system (RAAS) inhibitors —studies known to have appropriately higher KD exclusion rates—decreased over time (20% versus 4% in the prior and contemporary eras, respectively; $P<0.01$), whereas the number of studies examining antiplatelet and percutaneous coronary intervention strategies surged. After excluding trials of RAAS inhibitors, the proportion of studies explicitly excluding patients with KD was similar in both eras (129 of 293 [44%] versus 57 of 122 [47%], $P=0.67$).

Contemporary-era trials more frequently cited as primary methods for exclusion the more accurate equations to estimate kidney function (*e.g.*, eGFR, creatinine clearance) (42 of 305 [14%] versus 3 of 153 [2%] for older trials, $P<0.01$). The more recent trials also were likelier than the older trials to report the proportion of patients with KD allocated to each arm (control and intervention) (68 of 305 [22%] versus 22 of 153 [14%], $P<0.05$), to report baseline kidney function for each group (71 of 305 [23%] versus 19 of 153 [12%], $P<0.01$), and to have KD subgroup analyses (56 of 305 [18%] versus 10 of 153 [7%], $P<0.01$).

Analysis

The proportion of contemporary studies (2006–2014) with KD representation was 10% higher than in older (1985–2005) studies, a trend found across multiple subgroups, including multicenter and large-scale trials. Still, nearly half of the contemporary CVD trials excluded patients with KD. Moreover, the overall increase in KD representation may be partially attributable to the significant decrease in the proportion of trials of RAAS inhibitors reported in the contemporary era compared with the earlier group of studies; when we considered only non–RAAS inhibitor trials, the observed proportion of participants with KD in CVD trials remained unchanged across time. This underrepresentation may reflect a general concern among trialists and drug manufacturers that including patients with KD in trials might diminish overall success rates of innovative therapies or reflect a lack of data from phase 1 and phase 2 studies for this patient population.

Despite the observed modest increase in enrollment of patients with KD in CVD trials, reported mortality rates in those with KD have remained discrepantly higher than the general population.[6] In fact, patients with KD continue to have one of the highest risks of observed mortality among those presenting with CVD, and yet they remain underrepresented in clinical trials. This is partially explained by reported contraindications or untested efficacy of otherwise potentially lifesaving therapies in patients with KD, as well as by concern that inclusion of patients with KD in trials may diminish overall efficacy rates. However, the available evidence strongly suggests that patients with KD who are not treated with typical cardiac interventions fare much worse than their treated counterparts, even after adjusting for comorbidities.[6]

Our analysis also demonstrates a heightened focus in recent years on the monitoring of kidney function within CVD studies. This is reflected by the observed increases in reporting of baseline kidney function, KD subgroup analyses, and the use of more reliable objective assessments of kidney function in place of subjective parameters. Similarly, re-

Table 1. Exclusion rates by subgroup, stratified by study era[a]

Variable	Contemporary Era (2006–2014), No. (%)		Prior Era (1985–2005[b]), No. (%)		*P* Value
	Trials	Explicit Exclusion of KD, Trials	Trials	Explicit Exclusion of KD, Trials	
Overall	305 (100)	139 (46)	153 (100)	86 (56)	0.04
Trial enrollment no. of patients					
100–499	114 (37)	56 (49)	40 (26)	15 (38)	0.20
500–999	65 (21)	29 (45)	23 (15)	14 (61)	0.23
≥1000	126 (41)	55 (44)	90 (59)	57 (63)	<0.01
Sites					
Single center	25 (8)	13 (52)	15 (10)	3 (20)	0.06
Multicenter	280 (92)	126 (45)	138 (90)	83 (60)	0.01
Location[c]					
United States/Canada	32 (10)	13 (41)	64 (42)	48 (75)	<0.01
Europe	123 (40)	55 (45)	77 (50)	28 (36)	0.76
Asia/Australia/other	21 (7)	8 (38)	12 (8)	10 (83)	0.03
Therapeutic class					
Thrombolytic	3 (1)	1 (33)	27 (18)	9 (33)	>0.99
PCI	89 (29)	26 (29)	31 (20)	11 (35)	0.51
Device (AICD/pacer)	25 (8)	4 (16)	7 (5)	3 (43)	0.16
RAAS inhibitor	12 (4)	10 (83)	31 (20)	29 (94)	0.31
β blocker	3 (1)	0 (0)	13 (8)	7 (54)	0.21
Antiplatelet agent	46 (15)	24 (52)	14 (9)	5 (36)	0.37
Anticoagulants	31 (10)	23 (74)	12 (8)	11 (92)	0.41
Statins	8 (3)	5 (63)	7 (5)	5 (71)	>0.99
Non-RAAS modulation	293 (96)	129 (44)	122 (80)	57 (47)	0.67
Funding source					
Industry	168 (55)	86 (51)	87 (57)	54 (62)	0.11
Government (NIH/VA)	27 (9)	11 (41)	31 (20)	14 (45)	0.80
Combination	58 (19)	22 (38)	17 (11)	11 (65)	0.06
Not specified	25 (8)	13 (52)	18 (12)	7 (39)	0.54
Journal					
NEJM	60 (20)	30 (50)	59 (39)	38 (64)	0.14
JAMA	39 (13)	17 (44)	12 (8)	6 (50)	0.75
Lancet	34 (11)	10 (29)	48 (31)	23 (48)	0.11
Circulation	33 (11)	15 (46)	12 (8)	10 (83)	0.04
JACC	57 (19)	23 (40)	11 (7)	2 (18)	0.19
Am. Heart Journal	17 (6)	4 (24)	6 (4)	6 (100)	<0.01
Euro. Heart Journal	37 (12)	24 (65)	5 (3)	1 (20)	0.14
Annals of IM	2 (1)	1 (50)	0	0	>0.99
Diagnostic category					
AMI/ACS	208 (68)	92 (44)	117 (76)	58 (50)	0.36
CHF	57 (19)	29 (51)	36 (24)	28 (78)	0.02

P values represent comparisons across groups. *P* value calculated using number of trials excluding KD not total trials. PCI, percutaneous coronary intervention; AICD, automated implantable cardioverter-defibrillator; NIH/VA, National Institute of Health/Veterans Affairs; NEJM, New England Journal of Medicine; JAMA, Journal of the American Medical Association; Am. Heart Journal, American Heart Journal; Euro. Heart Journal, European Heart Journal; Annals of IM, Annals of Internal Medicine; AMI, acute myocardial infarction; ACS, acute coronary syndromes; CHF, congestive heart failure.

[a]Only comparable data were included.

[b]Data from the 1985–2005 era were adopted from the study by Coca *et al.*[5]

[c]United States/Canada versus Europe used in chi-squared analysis.

cent cardiovascular practice guidelines have placed greater emphasis on patients with KD presenting with CVD.[7–10] Overall, most practice guidelines have given increased weight to KD assessment, while noting the lack of high-quality data and the need for more research focusing on this increasing segment of the CVD population.

This report of KD representation in CVD trials is the most comprehensive to date and included journals with the highest effect factors. Although our findings are comparable to those of a recent systematic review by Konstantinidis *et al.* that evaluated the rate of KD inclusion among CVD trials and reported continued underrepresentation of KD participants in such trials,[4] our analysis also points out the overall greater emphasis on kidney function monitoring. In addition, it incorporates atrial fibrillation and stable coronary artery disease trials, which are increasingly expanding areas of CVD research. These trials, identified using broadened search terms, were not

Table 2 Representation of patients with kidney disease in cardiovascular trials, stratified by study era

Variable	Contemporary Era (2006–2014), No. (%)	Prior Era (1985–2005[a]), No. (%)	*P* Value
Quantitative thresholds for exclusion[b]			
Serum Cr >1.5–2.0 mg/dl	20 (7)	19 (12)	0.15
Serum Cr >−2.1 to 2.9 mg/dl	27 (9)	24 (16)	0.14
Serum Cr >−3.0 mg/dl	23 (8)	16 (10)	0.72
eGFR/Cr Cl levels	42 (14)	3 (2)	<0.01
Nonspecific exclusion	31 (10)	24 (16)	0.34
Nonspecific exclusion criteria[b]			
Need for HD only	10 (3)	n/a	n/a
Known kidney insufficiency	3 (1)	n/a	n/a
Severity only	15 (5)	n/a	n/a
Contraindication to meds only	3 (1)	n/a	n/a
Trials reporting proportion of patients with KD allocated to each arm	68 (22)	22 (14)	<0.05
Trials reporting baseline Cr or eGFR given for each group	71 (23)	19 (12)	<0.01
Trials with subgroup analysis on patients with KD	56 (18)	10 (7)	<0.01

P values represent comparisons across groups. *P* value calculated using number of trials excluding KD not total trials. eGFR calculated either *via* Modification of Diet in Renal Disease equation or Cockroft–Gault equation. Cr, creatinine; Cr Cl, creatinine clearance; HD, hemodialysis; n/a, not applicable.
[a]Data from the 1985–2005 era were adopted from the study by Coca *et al.*[5]
[b]Includes overlaps.

included in a 2006 report by Coca *et al.*[5] Finally, our analysis focused on randomized trials, allowing for analysis of higher-quality data, and relied on manual extraction of data and their validation by two independent investigators.

Limitations of our study include the possibility that important CVD clinical trials may have been published in journals other than the ones we examined. In addition, the exclusion of patients with KD in some RCTs may have been justified from a pharmacologic standpoint (*e.g.*, kidney adverse events), and our report does not allow ascertainment of appropriateness of KD exclusion.

In summary, we found a modest increase in the inclusion of KD participants in CVD clinical trials during the contemporary era. However, this trend is driven primarily by a decrease in the proportion of RAAS inhibitors trials during that period, with no increase in KD participation seen among non–RAAS inhibitor trials. Given the increasing prevalence of KD among patients presenting with CVD, the judicious broadening of trial eligibility is warranted.

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DISCLOSURES

None.

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