Coronary Revascularization With or Without Cardiopulmonary Bypass in Patients With Preoperative Nondialysis-Dependent Renal Insufficiency

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Background. Preoperative renal insufficiency is a predictor of acute renal failure in patients undergoing conventional coronary artery bypass grafting. Off-pump coronary artery bypass operations have been shown to reduce renal dysfunction in patients with normal renal function, but the effect of this technique in patients with preoperative nondialysis-dependent renal insufficiency is unknown.

Methods. From June 1996 to December 1999, data of 3,250 consecutive patients undergoing coronary artery bypass grafting were prospectively entered into the Patient Analysis & Tracking Systems (PATS, Dendrite Clinical Systems, London, UK). Two hundred and fifty-three patients with preoperative serum creatinine more than 150 μmol/L were identified (202 patients on-pump, 51 patients off-pump), and clinical outcomes were analyzed. Serum creatinine and urea, in-hospital mortality, and morbidity were compared between groups. The association of perioperative factors with acute renal failure was investigated by multiple logistic regression analysis.

Results. Preoperative characteristics were similar between the groups. Mean number of grafts was 2.9 ± 0.8 and 2.3 ± 0.8 in the on-pump and off-pump groups, respectively ($p < 0.0001$). Comparison between groups showed a significantly higher incidence of stroke, inotropic requirement, blood loss, and transfusion of red packed cell and platelets in the on-pump group (all $p < 0.05$). Postoperative serum creatinine and urea were higher in the on-pump group with a significant difference at 12 hours postoperatively ($p < 0.05$). Logistic regression analysis identified cardiopulmonary bypass, serum creatinine level 60 hours postoperatively, inotropic requirement, need for intraaortic balloon pump, transfusion of red packed cell, and hours of ventilation as predictors of postoperative acute renal failure.

Conclusions. This study suggests that off-pump coronary artery bypass operations reduce in-hospital morbidity and the likelihood of acute renal failure in patients with preoperative nondialysis-dependent renal insufficiency undergoing myocardial revascularization.

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The incidence of acute renal failure (ARF) requiring dialysis after open-heart operations is relatively low (1% to 5%) [1–4], but it is associated with a mortality rate up to 60% [1].

The etiology is multifactorial and includes advanced age, history of preexisting renal insufficiency, left ventricular impairment, prolonged aortic cross-clamp, and cardiopulmonary bypass (CPB) [5, 6]. Factors related to the conduct and management of CPB are the systemic inflammatory response, hypoperfusion, loss of pulsatile perfusion, and myocardial dysfunction [1, 7–9].

Strategies directed toward reduction of postoperative ARF have focused mainly on the use of drugs like dopamine, mannitol, and frusemide with controversial results [1, 2, 8, 9].

Myocardial revascularization with off-pump coronary artery bypass (OPCAB) operation has been shown to minimize renal injury in elective patients with normal preoperative renal function [10].

This retrospective analysis of prospectively collected data investigates the incidence and risk factors for ARF in patients with preoperative nondialysis-dependent renal insufficiency undergoing coronary artery bypass grafting with or without CPB and cardioplegic arrest.

Material and Methods

Patient Selection

From June 1996 to December 1999, 3,250 patients underwent coronary artery bypass grafting at our institution (30 days in-hospital mortality, 1.4%). A standard set of perioperative data were collected prospectively for all patients and entered into the Patient Analysis & Tracking Systems (PATS, Dendrite Clinical Systems, London, UK).

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The database includes 5 different sections to be filled in consecutively by anesthetist, surgeon, intensive care unit, high dependency unit, and ward nurses. Two hundred and fifty-three patients with preoperative serum creatinine more than 150 μmol/L were identified; these included 202 patients undergoing conventional coronary artery bypass grafting and 51 patients undergoing OPCAB operations. Patients with preoperative chronic renal failure requiring hemodialysis, peripheral vascular disease, emergency operation, and reoperation were excluded. None of the patients in the study had undergone angiographic investigations in the 4 weeks before the operation.

Allocation to on-pump and off-pump operations was based on the preference and expertise of the surgeons carrying out the operations, and also during the early part of data collection when experience was still being gained with off-pump techniques on coronary anatomy and number of grafts required.

Anesthetic Technique

Anesthetic technique was standardized for all patients. This consisted of intravenous anesthesia with propofol infusion at 3 mg/kg/hr combined with remifentanil infusion at 0.5 to 1 μg/kg/min. Neuromuscular blockade was achieved by 0.1 to 0.15 mg/kg pancuronium bromide or vecuronium and the lungs ventilated to normocapnia with air and oxygen (45% to 50%) without positive end expiratory pressure. In the on-pump group metaraminol or phentolamine were used to maintain the systemic perfusion pressure at a mean of 60 mm Hg. In the off-pump group mean arterial pressure of 60 mm Hg or above was maintained with increments of metaraminol 0.5 to 1.0 mg or volume as dictated by the hemodynamic condition.

Heparin and Protamine Management

In the on-pump group, heparin was given at a dose of 300 IU/kg to achieve a target activated clotting time of 480 seconds or above before commencement of CPB. The activated clotting time was monitored during the bypass period (every 15 minutes), and an additional 3,000 IU of heparin was administered if required. In the off-pump group, heparin (100 IU/kg) was administered before the start of the first anastomosis to achieve an activated clotting time of 250 to 350 seconds. On completion of the operation, protamine was given to reverse the effect of heparin and return the activated clotting time to preoperative levels.

Surgical Technique

GROUP A: ON-PUMP. Cardiopulmonary bypass was instituted using ascending aortic cannulation and two stage venous cannulation of the right atrium. A standard circuit was used, which included a 40-micron filter, a Stockert roller pump (B. Braun, Melsungen, Germany), and a hollow fiber membrane oxygenator (Sorin Biomedica, Midhurst, UK). The extracorporeal circuit was primed with 1,000 mL of Hartman's solution, 500 mL of Gelofusine, 0.5 g/kg mannitol, 7 mL of 10% calcium gluconate, and 6,000 IU of heparin. Nonpulsatile flow was used, and flow rates throughout bypass were 2.4 L/m^2/min. Intraoperative ultrafiltration was used if the base line value of serum creatinine was 300 μmol/L or greater. Systemic temperature was kept between 34°C and 36°C. Myocardial protection was achieved by using intermittent anterograde hyperkalemic warm blood cardioplegia [11].

On completion of all distal anastomoses, the aortic cross clamp was removed and the proximal anastomosis was performed with partial clamping.

GROUP B: OFF-PUMP. The method of exposure and stabilization to perform the anastomosis consisted of the technique previously described by our group [12]. The target vessel was exposed and snared above the anastomotic site using a 4-0 Prolene (Ethicon, Somerville, NJ) suture with a soft plastic snugger to prevent coronary injury. The coronary artery was then opened and the anastomosis was performed. Visualization was enhanced by using a surgical blower-humidifier (Model SSVW-002, Surgical Site Visualization Wand, Research Medical Inc, Midvale, UT) with a gas and a fluid administration set connected to a regulated gas source of medical air. An intracoronary shunt (Anastoflo Intravascular Shunt, Research Medical Inc, Midvale, UT) was used only in cases of relative electrocardiographic or hemodynamic instability or excessive bleeding during the construction of the anastomosis. As a safety measure the CPB machine was kept with the circuit mounted, but not primed dry.

Clinical Data Collection, Monitoring, and Definitions

Patients' characteristics, intraoperative data, and postoperative data were entered prospectively into the PATS system. In-hospital mortality was defined as any death occurring within 30 days of operation. Heart rate, rhythm, and ST segment elevations were continuously monitored and displayed on a monitor inclusive of an automated detector of segment elevations and arrhythmia during the first 72 hours postoperatively (Solar 8000 Patient Monitor, Marquette Medic Systems, Milwaukee, WI). Perioperative myocardial infarction, ST segment elevation changes, pacing, arrhythmias, and inotropic requirement were recorded and defined as previously reported [11]. Renal complication included ARF as defined by the requirement of hemodialysis. Postoperative blood loss was defined as total chest tube drainage [13]. Neurologic complication included permanent and transient stroke. Pulmonary complication included chest infection, ventilation failure, reintubation, and tracheostomy [11]. Finally, infective complication included septicemia, and sternal and leg wound infection as defined by positive culture requiring antibiotic therapy.

Biochemical Markers

The time course of perioperative serum creatinine and urea levels was reviewed at base line and at 1, 12, 36, and 60 hours postoperatively.

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Table 1. Logistic Regression Analysis[a]

Variable	Value	Standard Error	t Statistic	Confidence Interval	Odds Ratio	p Value
Intercept	−7.37	1.17	−6.25	(−9.68, −5.06)	...	0.000
Cardiopulmonary bypass plus cardioplegic arrest	0.9	0.45	1.95	(0.001, 1.80)	2.5	0.05
Serum creatinine at 60 hrs (μmol/L)	0.017	0.0028	6.16	(0.01, 0.02)	1.02	< 0.0001
Modest inotropic requirement[b]	0.88	0.38	2.28	(0.13, 1.64)	2.4	0.023
Use of intraaortic balloon pump	1.317	0.432	3.043	(0.47, 2.17)	3.7	0.003
Transfusion of red packed cell	−0.839	0.402	−2.08	(−1.63, −0.05)	0.43	0.038
Intubation time	0.0703	0.029	2.403	(0.01, 0.13)	1.07	0.017

[a] The values of the coefficients, their standard errors, associated t statistic, confidence interval, and p value are reported. [b] Dopamine ≤ 7 μg/kg/min.

Statistical Analysis

The χ^2 test and t test were used to look for any differences on categorical and continuous variable between patients in the on-pump and off-pump groups. Logistic regression analysis was used to investigate the association of preoperative, intraoperative, and postoperative variables with postoperative ARF. The best model given in the results and in Table 1 was obtained by a backward elimination approach guided by χ^2 statistics and sometimes Mallow's Cp and residual examination [14]. Factors reported as predictors of ARF by other investigators are age at operation, preoperative mild renal insufficiency, hypertension, diabetes mellitus, left ventricular dysfunction, cardiopulmonary bypass (inclusive of cardioplegic arrest), intubation time, and blood transfusion. As our study was observational and not randomized to mitigate for the effects of any bias on observed covariates, we repeated our analyses on groups of patients subclassified according to propensity score as described by others [15, 16]. For continuous data, repeated measures of analysis were used to assess differences over time between groups, and the Bonferroni test was used to assess the differences within the groups. The statistical package S-Plus (Insightful Corporation, Seattle, WA) was used to fit and evaluate the models.

Results

Baseline characteristics are shown in Table 2. The two groups were similar with respect to age, gender, diabetes mellitus, hypertension, angina class, ejection fraction, and Parsonnet score. The off-pump group showed a significantly higher percentage of patients with history of cerebrovascular accidents. Mean number of grafts was 2.9 ± 0.8 and 2.3 ± 0.8 in the on-pump group and off-pump group, respectively ($p < 0.0001$). Postoperative clinical outcome is reported in Table 3. There were 16 deaths (7.9%) in the on-pump group and 3 deaths (5.9%) in the off-pump group.

Patients in the on-pump group showed a significantly higher incidence of stroke, inotropic requirement, blood loss, and postoperative transfusion of red packed cell and platelets compared with the off-pump group. Furthermore, 32 patients (15.8%) in the on-pump and 3 patients (5.9%) in the off-pump group experienced postoperative ARF requiring dialysis ($p = 0.06$, on-pump vs off-pump).

Table 2. Baseline and Intraoperative Characteristics[a]

Variable	On-Pump (n = 202)	Off-Pump (n = 51)	p Value[b]
Age (y)	67.8 ± 7.4	68.2 ± 10.4	0.73
Sex (male/female)	178/24	44/7	0.71
Canadian class			0.61
I	21 (10.4)	7 (13.7)	...
II	83 (41.0)	15 (29.4)	...
III	76 (37.6)	22 (43.1)	...
IV	22 (10.9)	7 (13.7)	...
Symptom status			0.36
Stable	77 (38.1)	23 (45.1)	
Unstable	125 (61.9)	28 (54.9)	
Previous myocardial infarction	111 (54.9)	28 (54.9)	0.99
Diabetes mellitus	42 (20.8)	9 (17.6)	0.6
Hypertension	126 (62.3)	30 (58.8)	0.64
Hypercholesterolemia	118 (58.4)	31 (60.7)	0.78
Respiratory complications	29 (14.3)	7 (13.7)	0.9
Previous cerebrovascular accident	19 (9.4)	11 (21.5)	0.016
Ejection fraction			0.94
Good (> 49%)	101 (50)	25 (49)	...
Fair (30%–49%)	70 (34.6)	17 (33.3)	...
Poor (< 30%)	31 (15.4)	9 (17.6)	...
Parsonnet score	10.3 ± 7.0	11.02 ± 6.4	0.5
Cardiopulmonary bypass time (min)	84.5 ± 30.1		...
Cross-clamp time (min)	45.1 ± 16.8		...
Graft/patient (n)	2.9 ± 0.8	2.3 ± 0.8	<0.0001
Graft distribution:			...
Internal mammary artery to LAD or diagonal branch of LAD graft	196 (97.0)	48 (94.1)	...
Saphenous vein to diagonal branch of LAD graft	71 (35.1)	15 (29.4)	...
Right coronary artery/posterior descending artery graft	138 (68.3)	22 (43.1)	...
Circumflex artery graft	134 (66.3)	20 (39.2)	...
Other arterial grafts[c]	46 (22.7)	12 (23.5)	...

[a] Data are presented as number of patients (percentage in parenthesis) or mean ± standard deviation. [b] Student t test or χ^2 test. [c] This included the use of left and right internal mammary artery and radial artery to vessels other than the LAD.

LAD = left anterior descending coronary artery.

Table 3. Postoperative Clinical Outcome[a]

Variable	On-Pump (n = 202)	Off-Pump (n = 51)	*p* Value
Deaths	16 (7.9)	3 (5.9)	0.62
Myocardial infarction	6 (2.9)	2 (3.9)	0.72
Inotropic requirement			0.009
Modest	65 (32.1)	7 (13.7)	
Significant	38 (18.8)	3 (5.9)	
Postoperative intraaortic balloon pump	18 (8.9)	3 (5.8)	0.48
Arrhythmias	67 (33.1)	10 (19.6)	0.06
SVT	52 (25.7)	7 (13.6)	0.07
VT/VF	9 (4.4)	1 (1.9)	0.41
Permanant pacemaker	6 (2.9)	2 (3.9)	0.72
Renal complications			
Acute renal failure/dialysis	32 (15.8)	3 (5.9)	0.06
Respiratory complications	34 (16.8)	5 (9.8)	0.21
Neurological complications (all)	19 (9.4)	2 (3.9)	0.2
Stroke	14 (6.9)	0 (0.0)	0.05
Transient ischemic attack	5 (2.47)	2 (3.9)	0.57
Gastrointestinal bleeding	7 (3.45)	0 (0.0)	0.17
Infective complications	15 (7.42)	3 (5.9)	0.69
Reopening for bleeding	9 (4.4)	2 (3.9)	0.88
Total blood loss (mL)	980 ± 429	793 ± 450	0.009
Postoperative transfusion requirement			
Red blood cell	1.89 ± 1.95	1.02 ± 1.61	0.001
Platelets	0.42 ± 0.89	0.04 ± 0.19	< 0.0001
Fresh frozen plasma	0.53 ± 1.34	0.31 ± 0.83	0.15
Intubation time (h)	12.5 ± 7.1	11.8 ± 9.6	0.6
Intensive care unit length of stay (d)	2.66 ± 3.48	2.36 ± 3.1	0.5
Hospital length of stay (d)	10.44 ± 6.7	10.31 ± 10.2	0.9

[a] Data are presented as number of patients (percentage in parenthesis) or mean ± standard deviation. Modest inotropic requirement = ≤ 7 μ/kg/min dopamine; significant inotropic requirement = adrenaline/enoximone.

SVT = supraventricular tachycardia; VF = ventricular fibrillation; VT = ventricular tachycardia.

The baseline values of creatinine and urea were similar between groups. Preoperative serum creatinine ranged from 150 to 336 μmol/L (mean, 177.1 ± 32.6) in the on-pump group with 3 patients more than 300 μmol/L who received ultrafiltration during the operation. In the off-pump group, serum creatinine ranged from 150 to 366 μmol/L (mean 182.6 ± 52.0), with 3 patients more than 300 μmol/L.

The perioperative release of serum creatinine and urea are reported in Figures 1 and 2. Comparison over time between groups showed significantly higher levels of serum creatinine and urea in the on-pump groups (both analysis of variance, $p < 0.05$). Comparisons at each time point between groups showed a significantly higher level of creatinine soon after operation and at 12 hours postoperatively (both, $p < 0.05$), and of urea at 12 hours postoperatively ($p < 0.05$) in the on-pump compared with the off-group. The mean change in serum creatinine at 60 hours postoperatively was 60 ± 89 and 23 ± 72 μmol/L in the on-pump and off-pump groups, respectively (p = 0.0027).

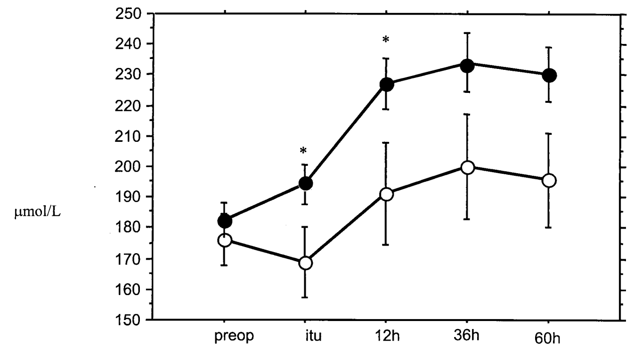

Fig 1. Perioperative serum creatinine level. (● = *on-pump;* ○ = *off-pump;* p < *0.05 analysis of variance). *p < 0.05 on-pump versus off-pump.* (h = *hours;* itu = *intensive therapy unit;* preop = *preoperative.)*

For the backward elimination, several models were fitted to the data with detailed model assessment. A stepwise deletion approach was initially taken to reduce the large number of variables in the model. Define p_i to be the probability of having renal complications for individual (i). Then the following model was found to fit the data well.

Log (p_i/[1-pi]) = −7.37 + 0.90 CPB plus 0.0176 creatinine at 60 hours plus 0.882 modest inotropic requirement plus 0.137 significant inotropic requirement plus 1.31 intraaortic balloon pump postoperatively minus 0.839 red packed cell transfusion plus 0.07 hours of ventilation.

The values of the coefficients, their standard errors, associated *t* statistic, confidence interval, odds, and *p* value are reported in Table 3. Serum creatinine at 60 hours postoperatively, CPB inclusive of cardioplegic arrest, modest inotropic requirement, intraaortic balloon pump, transfusion of red packed cell, and intubation time were all found to be predictors of postoperative ARF. Particularly patients who experienced CPB increased their odds of renal complications by a factor of 2.5 taking into account all of the other variables.

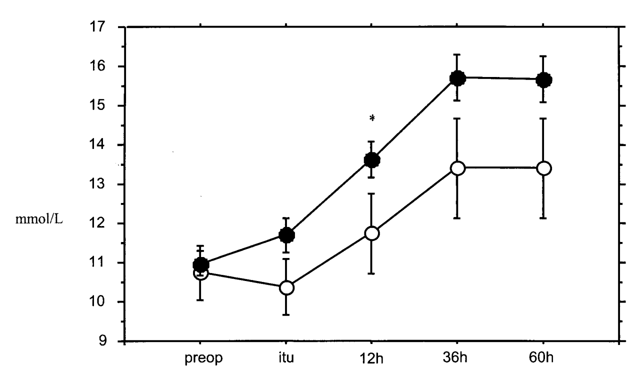

Fig 2. Perioperative serum urea level. (● = *on-pump;* ○ = *off-pump;* p < *0.05 analysis of variance). *p < 0.05 on-pump versus off-pump.* (h = *hours;* itu = *intensive therapy unit;* preop = *preoperative.)*

Comment

The development of acute postoperative renal insufficiency after cardiac operations has been blamed on CPB as the result of hemodynamic factors or toxic insults on the kidney, or both [1, 2, 4, 6–9, 17]. Moderate transient impairment of renal function (plasma creatinine level greater than 1.5 mg/100 mL but less than 5.0 mg/100 mL) occurs after 30% of cardiac operations performed with CPB and is associated with a reported mortality rate varying from 7% to 38% [1, 18]. When acute renal failure after CPB is severe enough to require dialysis it is said to be highly lethal (death rate, 60% to 100%) [17]. This is in marked contrast to the 1% to 2% mortality rate observed in patients whose cardiac operation is not complicated by acute renal failure. Protective attempts to prevent renal dysfunction have focused on overall hemodynamic control and hydratation, optimization of perfusion pressure during CPB, use of mannitol, frusemide, and dopamine infusion [3, 19, 20]

The off-pump coronary artery bypass operation is a relatively new surgical procedure and may be considered the best model of pulsatile perfusion, which at the same time avoids the use of CPB and its side effects. In a prospective randomized study performed at our institution, we showed that patients undergoing OPCAB operations had significantly less deterioration in renal function than those undergoing conventional coronary artery bypass grafting [10]. However, there is no evidence in the literature on whether these benefits may also apply to patients with preoperative nondialysis-dependent renal insufficiency.

The level of 150 μmol/L of serum creatinine chosen as a cut off to define patients with preoperative nondialysis-dependent renal insufficiency was used in the study in accordance with previous works published in the literature [21]. A review of risk factors for postoperative renal dysfunction after conventional cardiac operation with CPB in 42,773 patients confirmed the strong predictive power of preoperative plasma creatinine in excess of 1.5 mg/dL as well as age, emergency surgery, peripheral and cerebral vascular disease, and reoperation [21]. Rao and associates [5] found that mild renal insufficiency, in the absence of dialysis, increased the risk of blood transfusion, lowered output syndrome, and prolonged the length of intensive care unit and hospital stays in patients undergoing coronary artery bypass grafting. Zanardo and associates [2] found that patients with preoperative renal failure showed a significantly higher morbidity and mortality rate than those without preexisting renal dysfunction.

In accordance with these studies we also found inotropic support, need for intraaortic balloon pump, transfusion of red packed cell, prolongation of ventilation, and serum creatinine levels at 60 hours postoperatively to be risk factors for ARF. However, to the best of our knowledge, this is the first study that demonstrates CPB inclusive of cardioplegic arrest is an independent predictor of postoperative ARF in patients with preoperative nondialysis-dependent renal insufficiency.

There are several possible explanations for these results. Cardiopulmonary bypass is known to activate inflammatory responses including the complement, coagulation, fibrinolytic, and kallicrein cascades. This, in turn, may lead to increased capillary permeability, accumulation of interstitial fluid, leukocytosis, and organ dysfunction [7, 22, 23]. Free plasma hemoglobin, elastase and endothelin, and free radicals including superoxide, hydrogen peroxide, and the hydroxyl radicals may be generated during CPB and may determine injury in the renal brush-border membrane [9]. Nonpulsatile flow, renal hypoperfusion, hypothermia, and duration of CPB are also thought to have adverse effects on renal function [8, 9, 24].

It is important to report that these results were obtained despite the advantageous effect of hemodilution on blood viscosity and improved renal plasma flow secondary to pump priming [25] and the use of mannitol in the prime in the on-pump group. This is reported to maintain glomerular capillary pressure and prevent tubular obstruction, protect against free radical induced injury to the renal brush border membrane, reduce ischemia-induced protein leakage across kidney vessel walls, and reduce plasma hydrogen peroxide free radicals [26].

The perioperative release of serum creatinine and urea in the off-pump group also showed a late increase when compared with base line. This suggests that anesthesia and surgical maneuvers may account for a certain degree of postoperative renal dysfunction.

Several limitations of the present study need to be discussed. The study design was observational and not a randomized one. However, the data analyzed in the present study were all prospectively collected and entered into a database as part of routine patient management at our institution. The analyses of this study were repeated on groups of patients subclassified according to propensity score [15, 16]. If anything, the subclassified groups indicated that benefits of OPCAB operation were greater than those stated in the Results section.

Finally, there was a significant difference in number of grafts between the two groups. This happened because we had a tendency to exclude patients with coronary disease involving the distal branches of the circumflex coronary artery at the beginning of our experiences with OPCAB operations.

In conclusion, our study suggests that OPCAB operations reduce in-hospital morbidity and the likelihood of ARF in patients with preoperative nondialysis-dependent renal insufficiency undergoing myocardial revascularization. We believe that a prospective randomized trial is now necessary to confirm our findings.

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