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Hypothermic Oxygenated Perfusion in Extended Criteria Donor Kidney Transplantation—A Randomized Clinical Trial

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ABSTRACT

Background: The role of machine perfusion after kidney transplantation (KT) in extended criteria donors (ECD) is unclear, and the current evidence in the literature remains controversial.

Methods: We present an open-label single center randomized trial where 109 patients undergoing KT with ECD grafts between January 2019 and December 2022 were randomized to receive kidneys treated with either hypothermic oxygenated perfusion (HOPE, $n = 54$) or static cold storage (SCS, $n = 55$) alone. The primary endpoint was the incidence of delayed graft function (DGF). The secondary endpoints included postoperative complications and graft function and survival in the first year after KT.

Results: The trial failed to meet its primary endpoint. DGF developed in 31 (57%) and 37 (67%) patients in the HOPE and SCS groups, respectively ($p = 0.3$). Posthoc analysis showed that HOPE was associated with a lower risk for DGF for grafts from donors aged 60 years or older (OR 0.32, 95% CI 0.12–0.87, $p = 0.026$) and in patients undergoing dual KTs (OR 0.22, 95% CI 0.06–0.87, $p = 0.031$).

Conclusions: HOPE does not reduce the rate of DGF after KT in ECD donors. However, HOPE appears to be associated with better outcomes in the case of older donors and dual KTs.

1 | Introduction

Kidney transplantation (KT) is the treatment of choice in patients with end-stage renal disease (ESRD). However, the shortage of available organs remains an important challenge in transplantation centers worldwide. The utilization of marginal grafts, such as Extended Criteria Donor (ECD) grafts, represents a valid strategy to address the discrepancy. ECD grafts offer better survival rates

Abbreviations: ARE, acute rejection event; CCI, comprehensive complications index; CIT, cold ischemia time; DBD, donor after brain death; DCD, donor after circulatory death; DGF, delayed graft function; ECD, extended criteria donor; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HOPE, hypothermic oxygenated perfusion; IRI, ischemic reperfusion injury; KDPI, kidney donor profile index; KDRI, kidney donor risk index; KT, kidney transplantation; MP, machine perfusion; PNF, primary non-function; SCS, static cold storage.

compared to replacement therapy in patients with ESRD but are at higher risk for developing delayed graft function (DGF) and primary non-function (PNF) after KT [1–3].

Machine perfusion (MP) has emerged in recent years as a promising option to the traditional static cold storage (SCS) preservation technique due to its potential ability to limit ischemic reperfusion injury. While the beneficial role of MP in liver transplantation is becoming more evident, its impact in KT remains unclear [4]. Recent randomized trials have failed to confirm the promising initial results published by Moers et al. [5–8]. However, it should also be noted that these studies are characterized by heterogeneous populations, MP techniques, and donor features.

The present is an open-label monocentric randomized study aimed at assessing the efficacy of hypothermic oxygenated perfusion (HOPE) and SCS in reducing the incidence of DGF after KT in ECD grafts from brain death donors (DBD).

2 | Material and Methods

2.1 | Trial Design and Oversight

The present is an open-label, monocentric randomized controlled trial conducted and overseen at the General Surgery and Transplantation Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy. Enrolled patients were stratified based on the cold ischemia time (CIT) during organ procurement and transportation (longer vs. shorter than 12 h) and randomized in a 1:1 ratio to receive grafts preserved with either HOPE (HOPE group) or SCS alone (SCS group) after cold storage during organ procurement and transportation.

The study was approved by the local Ethics Committee (Application Number 215/2018/Sper/AOUBo), and the original protocol has been previously published [9]. The CONSORT guidelines were followed to report the trial [10]. The authors were responsible for the implementation of the trial, collection, and analysis of the data. All the authors vouch for the accuracy and completeness of the data and the fidelity of the trial to the protocol.

2.2 | Donor and Patient Selection

Patients 18 years or older undergoing KT and receiving ECD grafts were eligible for the study. ECD grafts were defined based on the United Network for Organ Sharing (UNOS) criteria: (a) donor age >60 years old, or (b) donor age <60 years old with at least two of the following risk factors: (i) death after cerebrovascular accident, (ii) history hypertension, and (iii) donor serum creatinine >1.5 mg/dL [11]. Kidney allocation was decided based on national and international guidelines. Grafts with biopsy scores between 0 and 3 were eligible for single KTs, while kidneys from the same donor with both biopsy scores between 4 and 6 were considered for dual KTs [12]. Written informed consent was obtained before randomization.

Exclusion criteria included: (a) donor age <18 years old, (b) combined transplantation, and (c) DCD grafts. DCD grafts were excluded due to the 20 min "no-touch" period before death declaration required by the Italian law, which makes machine perfusion mandatory. In addition, during the COVID-19 pandemic, there was an outbreak of severe SARS-COV2 infections in the Nephrology Unit, where patients are transferred after KT, resulting in significantly higher morbidity and mortality. Thus, enrolment between the 1st of March 2020 and the 31st of June was suspended.

2.3 | Hypothermic Oxygenated Perfusion

Grafts were perfused with the Vitasmart device (Bridge to Live, DG, USA), which is exclusively designed for ex vivo perfusion of abdominal organs. MP was performed in the operating room from the start of the back-table preparation to implantation. Kidney grafts were perfused through the renal artery at a pressure of 25–30 mmHg. Perfusion started with a flushing phase with new oxygenated perfusion fluid to remove waste products and residual microthrombi, followed by a continuous phase till implantation. The minimum perfusion time was 2 h.

2.4 | Endpoint Measures

The primary endpoint of the study was the incidence of delayed graft function. DGF was defined as the need for replacement therapy in the first week after transplantation. Cases requiring dialysis on the first postoperative day due to hyperkalemia or volume subtraction were not considered as DGF.

The secondary endpoints were the duration of DGF, defined as the time from the first to the last dialysis, rate of PNF, defined as the irreversible graft dysfunction with graft loss, length of hospital stay, serum creatinine and estimated Glomerular Filtration Rate (eGFR) at 1, 3, 6, and 12 months after KT, rate of acute rejection events (ARE) and postoperative complications (vascular thrombosis, ureteral stenosis), as well as graft and patient survival at 1 year from KT. Graft loss was defined as patient death or irreversible graft injury requiring replacement therapy. Functional DGF was defined as the failure of serum creatinine to decrease by at least 10% for 3 days consecutively in the first week after KT, independently from dialysis [13].

2.5 | Statistical Analysis

Statistical analysis was carried out using the STATA software version 18.0 (Stat Corp., College Station, TX, USA). The sample size was calculated using the primary endpoint estimating a reduction of DGF rates from 50% in the SCS group to 25% in the HOPE group, accounting for a drop-out of 5% ($\alpha = 0.05$, power 80%). All endpoints were specified in the original protocol. Chi-square and Fisher exact tests were used to compare categorical variables, while parametric and non-parametric tests were used for continuous variable accordingly. In patients undergoing dual KT, cold ischemia and MP time were defined as the mean values between the two grafts. Post-hoc analysis to identify risk factors for DGF and graft loss at 12 months was performed using logistic regression. The final multivariate model was built in a backwards stepwise fashion, including only variables with $p < 0.1$ in the univariate analysis. High-risk groups in the post-hoc analysis

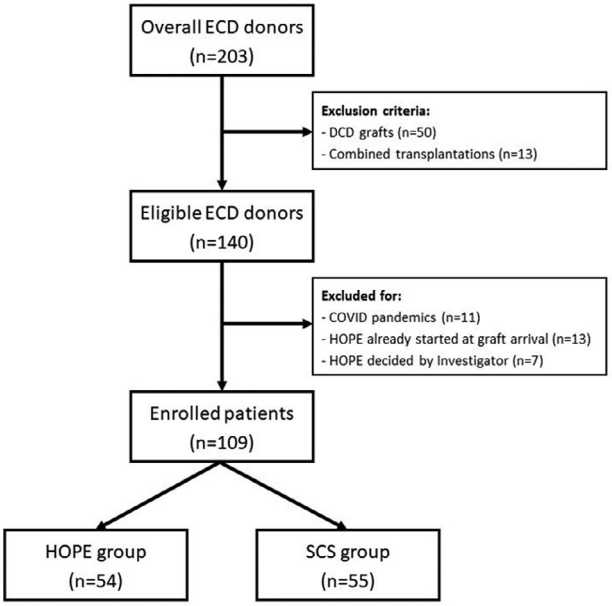

FIGURE 1 | CONSORT flow diagram for patient enrollment and randomization.

were selected from the multivariate analyses and relevant clinical variables. The optimal cut-off to define high-risk groups was defined at Youden's index in case of cold ischemia time. The threshold for statistical significance was set at $p < 0.05$.

3 | Results

A total of 203ECD grafts between the 1st of January 2019 and 31st of December 2022 were assessed for enrollment (Figure 1), from which 63 were excluded according to the pre-established exclusion criteria (DCG graft $n = 50$, combined transplantation $n = 13$). Among eligible grafts, 11 were excluded due to the COVID-19 pandemic's suspension and 20 because HOPE was either already started at arrival after procurement by another team ($n = 13$) or initiated by the Surgeon's decision ($n = 7$). A total of 109 patients were included in the final cohort and randomized in the HOPE ($n = 54$) and SCS group ($n = 55$). The baseline recipient, donor, and transplantation characteristics are shown in Table 1. There were no significant differences in demographic and clinical features between the two groups. Detailed donor biopsy scores are shown in Table S2.

Primary and secondary endpoint analyses are shown in Table 2. The trial failed to meet its primary endpoint. DGF developed in 31 (57%) and 37 (67%) patients in the HOPE and SCS groups ($p = 0.288$), respectively. The HOPE group was associated with shorter DGF duration and acute rejection rates (7% vs. 15%), although the differences were not significant ($p = 0.339$ and $p = 0.234$, respectively). Also, both groups were comparable in terms of PNF rate, renal function (serum creatinine and eGFR) at 1, 3, 6, and 12 months, as well as graft and patient survival at 1 year. Grade 3 or higher postoperative complications were similar between groups, although CCI was higher in the SCS group ($p = 0.048$).

Post-hoc analysis to identify risk factors for DGF and graft loss at 1 year is shown in Tables 3 and 4. DGF was associated with longer replacement therapy prior to KT (OR 1.020, 95% CI 1.002–1.037, $p = 0.025$) and cold ischemia time (OR 1.002, 95% CI 1.000–1.004, $p = 0.027$). The only significantly independent factor associated with graft loss at 12 months was the occurrence of DGF in the postoperative period (OR 10.370, 95% CI 1.309–82.146, $p = 0.027$).

Additional subgroup analysis explored the role of HOPE in high-risk patients (Table S1). HOPE was significantly associated with lower rates of DGF in grafts from donors >60 years old (OR 0.32, 95% CI 0.12–0.87, $p = 0.026$) and dual KT (OR 0.22, 95% CI 0.06–0.87, $p = 0.031$). HOPE appeared to be beneficial also in case of CIT >540 min, but the association did not reach statistical significance ($p = 0.076$).

4 | Discussion

Marginal grafts have been used to address the shortage of available organs for KT in patients with ESDR at the risk of higher graft dysfunction. The reported rates of DGF in literature vary between 30% and 60% [2, 3, 14–16]. In our cohort, 61% of the patients developed DGF. The rate of functional DGF calculated on the serum creatinine levels in the first post-transplant week was similarly set at 66%. The high rate of DGF can be explained by the relatively aggressive attitude when indicating dialysis after KT adopted in our Centre, as well as by the lower quality of grafts utilized. In fact, the median Kidney Donor Profile and Risk Index (KDPI and KDRI, respectively) were higher compared to analogue studies [6]. Also, this is the first randomized trial not to exclude dual KTs. The lower quality of the grafts, added to the complexity of dual KT, increase the risk of complications, and such marginal organs might not be offered for transplantation in all Centers. However, the comparable outcomes observed in our cohort show that they can be safely utilized in experienced Centers and further widen the pool of available organs.

The association between ischemic reperfusion injury (IRI) and graft dysfunction has been well established. In recent years, machine perfusion has been used ever more increasingly due to its ability to limit IRI and potentially improve graft function [17–19]. A randomized trial conducted by the Authors evidenced the positive impact of HOPE after liver transplantation in terms of early allograft dysfunction and graft survival [20]. Other studies have supported the results, as shown in a recent meta-analysis [4]. However, the evidence on the role of MP in KT is still limited. We conducted a randomized trial to evaluate the impact of HOPE in the development of DGF after KT of ECD grafts. The study failed to meet its primary endpoint. HOPE was associated with a lower rate of DGF (57% vs. 67%), but the difference was not statistically significant. Our results are in line with the latest similar studies. The encouraging results published initially by Moers et al. in 2009 have not been confirmed by more recent randomized trials [5]. Husen et al. randomized ECD grafts to either HOPE or SCS and found no difference between the two groups in terms of DGF or graft survival [6]. Hosgood et al. published similar results when comparing normothermic MP perfusion to SCS in DCD grafts [8]. The COMPARE trial evidenced a positive impact of oxygenated MP compared to standard MP on acute rejection events and graft survival, although there was no benefit on DGF rates [7].

TABLE 1 | Recipient, donor, and transplant characteristics.

	Total ($n = 109$)	HOPE group ($n = 54$)	SCS group ($n = 55$)	p value
Recipient				
Age (years)	60 (53–66)	61 (55–67)	59 (50–66)	0.3
Gender (male)	62 (57%)	32 (59%)	30 (55%)	0.6
BMI (kg/m^2)	24.7 (22.7–26.3)	25.1 (23.3–27.4)	24.5 (21.4–25.6)	0.046
Nephropathy				0.1
Congenital/metabolic disorder	8 (7%)	4 (7%)	4 (7%)	
Diabetic nephropathy	3 (3%)	2 (4%)	1 (2%)	
Glomerular disease	41 (38%)	18 (33%)	23 (42%)	
Tubular/interstitial disease	2 (2%)	2 (4%)	0 (0%)	
Hypertensive angiosclerosis	11 (10%)	8 (15%)	3 (5%)	
Polycystic kidney disease	20 (18%)	8 (15%)	12 (22%)	
Uncertain	4 (4%)	4 (7%)	0 (0%)	
Other	20 (18%)	8 (15%)	12 (22%)	
Dialysis duration (months)	43 (30–64)	43 (32–72)	42 (25–59)	0.2
First transplant (Yes vs. No)	101 (93%)	49 (94%)	52 (95%)	0.5
Donor				
Age (years)	66 (59–76)	69 (62–76)	64 (57–76)	0.1
Gender (male)	49 (45%)	19 (35%)	30 (55%)	0.040
BMI (kg/m^2)	25.3 (22.9–27.8)	25.0 (22.9–27.8)	25.8 (22.9–28.4)	0.9
Cause of death				0.7
Hypoxia	7 (6%)	2 (4%)	5 (9%)	
Cerebrovascular injury	83 (76%)	43 (79%)	40 (73%)	
Head trauma	17 (16%)	8 (15%)	9 (16%)	
Other	2 (2%)	1 (2%)	1 (2%)	
Creatinine (mg/dL)	0.78 (0.60–0.93)	0.76 (0.59–0.91)	0.79 (0.64–0.98)	0.1
Hypertension (Yes vs. No)	72 (67%)	35 (65%)	37 (69%)	0.7
Diabetes mellitus (Yes vs. No)	12 (11%)	6 (11%)	6 (11%)	1.0
Biopsy score				
Single KT	3 (2–3)	3 (2–3)	2.5 (2–3)	0.3
Dual KT	5 (4–5.5)	5 (4–5)	5 (4–6)	0.4
KDRI	1.52 (1.22–1.92)	1.61 (1.34–1.93)	1.42 (1.16–1.91)	0.1
KDPI	0.88 (0.70–0.97)	0.91 (0.78–0.97)	0.83 (0.65–0.97)	0.1
Transplant				
Dual KT (Yes vs. No)	44 (40%)	22 (41%)	22 (40%)	0.9
Cold ischemia time (min)	730 (588–869)	780 (640–865)	690 (545–870)	0.1
HOPE (min)	151 (112–270)	151 (112–270)	—	—
Induction				0.2
Thymoglobulin	41 (38%)	16 (30%)	25 (45%)	
Basiliximab	63 (58%)	34 (64%)	29 (53%)	
Both	4 (4%)	3 (6%)	1 (2%)	
Clavien-Dindo ≥3b	13 (12 %)	8 (15%)	5 (9%)	0.4
CCI	20.9 (8.7–29.6)	20.9 (0–26.2)	20.9 (8.7–29.6)	0.048

Note: Continuous variables are shown in median (interquartile) values.

Abbreviations: HOPE, hypothermic oxygenated perfusion; SCS, static cold storage; BMI, body mass index; KT, kidney transplantation; KDRI, kidney donor risk index; KDPI, kidney donor profile index; CCI, comprehensive complications index.

TABLE 2 | Primary and secondary outcomes analysis.

	Total ($n = 109$)	HOPE ($n = 54$)	SCS ($n = 55$)	p value
DGF	66 (61%)	31 (57%)	37 (67%)	0.3
PNF	7 (6%)	3 (6%)	4 (7%)	0.7
DGF duration (days)	7 (4–14)	5 (3–15)	8 (6–14)	0.4
Functional DGF	72 (66%)	34 (63%)	38 (69%)	0.5
Acute rejection	12 (11%)	4 (7%)	8 (15%)	0.2
Length of hospital stay (days)	19 (14–27)	18 (14–27)	20 (14–27)	0.4
Complications				
ureteral stenosis	6 (6%)	3 (6%)	3 (6%)	0.9
vascular thrombosis	5 (5%)	2 (4%)	3 (5%)	0.7
Graft loss at 1 Year	15 (14%)	9 (17%)	6 (11%)	0.4
Creatinine (mg/dL) at 1 Month ($n = 100$)	1.68 (1.30–2.42)	1.66 (1.28–2.55)	1.68 (1.38–2.36)	0.5
eGFR (mL/min) at 1 Month ($n = 100$)	40 (29–57)	44 (30–60)	38 (28–54)	0.4
Creatinine (mg/dL) at 3 months ($n = 88$)	1.62 (1.32–2.14)	1.63 (1.14–2.14)	1.60 (1.38–2.15)	0.4
eGFR (mL/min) at 3 months ($n = 88$)	46 (33–55)	50 (35–63)	41 (30–51)	0.1
Creatinine (mg/dL) at 6 months ($n = 80$)	1.65 (1.27–2.28)	1.71 (1.29–2.11)	1.50 (1.23–2.38)	0.8
eGFR (mL/min) at 6 months ($n = 80$)	46 (31–54)	45 (31–54)	47 (32–54)	0.8
Creatinine (mg/dL) at 12 months ($n = 78$)	1.53 (1.19–2.02)	1.53 (1.17–1.88)	1.53 (1.20–2.17)	0.6
eGFR (mL/min) at 12 months ($n = 78$)	48 (34–60)	50 (40–60)	45 (31–61)	0.2

Note: Continuous variables are shown in median (interquartile) values.
Abbreviations: DGF, delayed graft function; PNF, primary non-function.

TABLE 3 | Uni- and multivariate logistic regression of predictive factors for delayed graft function.

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
Age (years)	1.0 (1.0–1.0)	0.9	—	—
Male gender (Yes vs. No)	1.4 (0.7–3.2)	0.4	—	—
BMI (kg/m^2)	1.0 (0.9–1.2)	0.9	—	—
Dialysis time (months)	1.02 (1.00–1.03)	0.030	1.02 (1.00–1.04)	0.025
First KT (Yes vs. No)	0.5 (0.1–2.8)	0.5	—	—
KDPI	1.3 (0.2–9.4)	0.8	—	—
KDRI	1.5 (0.6–3.7)	0.3	—	—
CIT (min)	1.00 (1.00–1.01)	0.050	1.00 (1.00–1.01)	0.027
HOPE (Yes vs. No)	0.7 (0.3–1.4)	0.3	—	—
HOPE time (min)	1.0 (1.0–1.1)	0.5	—	—
Dual KT (Yes vs. No)	1.3 (0.6–2.9)	0.5	—	—

Abbreviations: BMI, body mass index; KT, kidney transplantation; KDPI, kidney donor profile index; KDRI, kidney donor risk index; CIT, cold ischemia time; HOPE, hypothermic oxygenated perfusion.

TABLE 4 | Uni- and multivariate logistic regression of predictive factors for graft loss at 12 months.

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	***p***	**OR (95% CI)**	***p***
Age (years)	1.1 (1.0–1.1)	0.6	—	—
Male gender (Yes vs. No)	3.52 (0.93–13.29)	0.063	—	—
BMI (kg/m^2)	0.9 (0.7–1.0)	0.1	—	—
Dialysis time (months)	1.01 (0.99–1.02)	0.075	—	—
First KT (Yes vs. No)	0.4 (0.1–2.4)	0.3	—	—
KDPI	5.5 (0.2–150.4)	0.3	—	—
KDRI	2.5 (0.8–8.0)	0.1	—	—
CIT (min)	0.99 (0.99–1.01)	0.4	—	—
HOPE (Yes vs. No)	1.6 (0.5–5.0)	0.4	—	—
Dual KT (Yes vs. No)	0.7 (0.2–2.2)	0.6	—	—
DGF (Yes vs. No)	10.37 (1.31–82.15)	0.027	10.37 (1.31–82.15)	0.027
Acute rejection (Yes vs. No)	1.3 (0.3–6.6)	0.8	—	—

Abbreviations: BMI, body mass index; KT, kidney transplantation; KDPI, kidney donor profile index; KDRI, kidney donor risk index; CIT, cold ischemia time; HOPE, hypothermic oxygenated perfusion; DGF, delayed graft function.

Although several metaanalyses seem to show a positive impact of MP on DGF, the correct interpretation of the data is rendered difficult by the lack of homogeneity among randomized trials in terms of graft features and perfusion techniques and duration [16, 21, 22].

The secondary endpoint analyses also showed similar outcomes between the two groups in terms of duration of DGF in days, acute rejection events, as well as graft function and survival at 12 months. Several authors have reported lower rates of ARE after MP. In our cohort, ARE was less frequent in the HOPE group, although the difference was not significant. We reported a longer median length of stay compared to similar studies. This can be explained by the fact that most of our recipients come from out of the region, and discharge is approved only after confirming the normal function of the graft. The rate of postoperative complications was comparable between the two groups. However, HOPE appeared to be associated with a better postoperative course due to shorter DGF duration and lower CCI score.

Post-hoc analysis was performed to investigate the risk factors for DGF and graft survival at 12 months. The main predictors of DGF reported in literature include graft features, cold ischemia time, and time of replacement therapy prior to KT [5, 23]. Several scores, such as KDPI and Kidney Donor Risk Index(KDRI), have been developed and validated to estimate the risk for DGF in clinical practice. In our cohort, DGF was associated with longer CIT and time of dialysis. Also, DGF was the only independent predictor of graft survival at 12 months. Literature on the impact of DGF on long term is still controversial with inconclusive results being reported [3, 24–26]. Our finding confirms the importance of preventing delayed graft function by optimizing graft procurement and preservation.

In addition, the role of machine perfusion in high-risk grafts was explored in the post-hoc analysis. HOPE was associated with lower DGF rates in the case of donors older than 60 years old and dual kidney transplantation. While the former correlation has already been described in literature [3], the latter was an interesting finding, that has not been previously reported, to our knowledge. Further prospective trials are required to better investigate the role of machine perfusion in dual KT.

The strongest point of the present study consists of its prospective nature, as well as the enrolment of more marginal grafts, including dual KTs, which is closer to real-life scenarios. The main limitation is the higher encountered DGF rate among both groups, rendering the original trial design underpowered in the post-hoc analysis and the actual sample sized inadequate to evaluated smaller differences in outcome

5 | Conclusion

We report a randomized trial aiming to evaluate the role of machine perfusion in ECD donors on delayed graft function after KT. HOPE was not associated with lower DGF rates in this cohort. However, lower CIT and the use of HOPE in the case of aged donors and dual KT appear to correlate to better outcomes, and further studies are required to explore the association.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data supporting the findings of this study are available from the corresponding author on request according to national and international legislation regarding privacy and data protection

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.