CORRESPONDENCE

Cold Perfusion vs. Static Cold Storage of Deceased-Donor Kidneys — at 10 Years

TO THE EDITOR: In 2009, we reported that hypothermic machine perfusion of kidneys from deceased donors starting after procurement reduced the risk of delayed graft function and that 1-year graft survival was significantly better with machine perfusion than with static cold storage.[1] In 2012, we reported that 3-year graft survival was also significantly better in machine-perfused kidneys, especially in kidneys obtained from expanded-criteria donors (those ≥60 years of age, or 50 to 60 years with compromised renal function or coexisting conditions).[2,3]

Since then, machine perfusion for preservation of deceased-donor kidneys has been adopted by many transplantation programs worldwide. Here, we report follow-up results 10 years after transplantation as a post hoc analysis of our multicenter trial.

Organ Recovery Systems provided funding for the first author, who coordinated the collection of the 10-year follow-up data. Organ Recovery Systems had no role in the trial design or data analysis and did not participate in the writing of this letter.

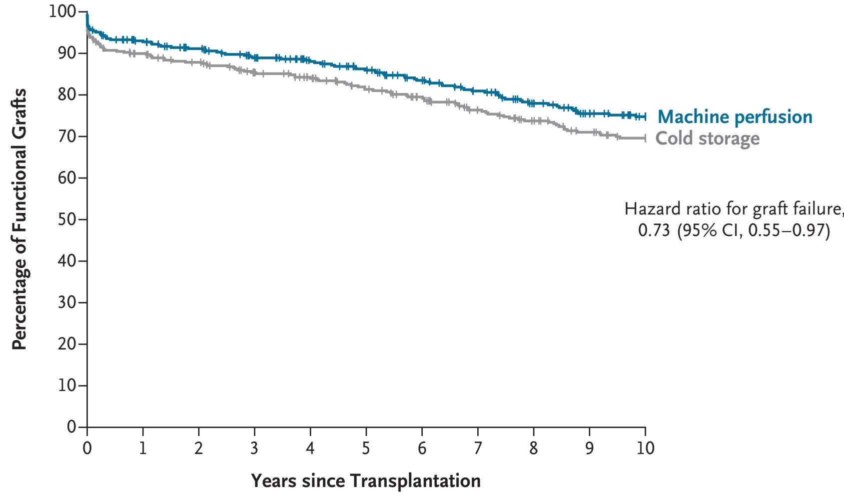
All 55 transplantation centers that originally participated in the trial were contacted to collect 10-year follow-up data. A total of 818 patients were involved in our original trial — 672 patients who had undergone transplantation and were included in the main analysis plus those in the two groups of patients in the officially extended trial population (80 patients who received paired kidneys from donors after circulatory death[1] and 66 patients who received kidneys from donors 65 years of age or older).[4] Statistical analyses were carried out as reported previously.[1]

The overall response to the request for follow-up data was 99%. We obtained complete 10-year data from 92% of the patients who received transplants; 6.7% of the patients were lost to follow-up. Machine perfusion appeared to be associated with a lower risk of graft failure during the 10 years after transplantation than cold storage. Within 10 years after transplantation, 88 of 409 grafts failed in the machine-perfusion group and 110 of 409 grafts failed in the cold-storage group (graft survival, 78.5% vs. 73.1%; adjusted hazard ratio for graft failure, 0.73; 95% confidence interval, 0.55 to 0.97) (Fig. 1A). Graft survival of kidneys from expanded-criteria donors[3] (276 kidneys) was 69.6% in the machine-perfusion group and 60.1% in the cold-storage group. Machine perfusion appeared to have no effect on graft survival of kidneys from standard-criteria donors (Fig. 1B). Patient survival at 10 years and estimated glomerular filtration rates of functioning kidney grafts at 10 years after transplantation were similar in the two trial groups (see Tables S1 through S3 and Figs. S1 through S4 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). Patients included in this trial remain representative of patients who have undergone kidney transplantation today (Table S4), which supports the generalizability of the results.

The results after 10 years suggest the possibility that machine perfusion may confer greater benefit in kidneys from expanded-criteria donors

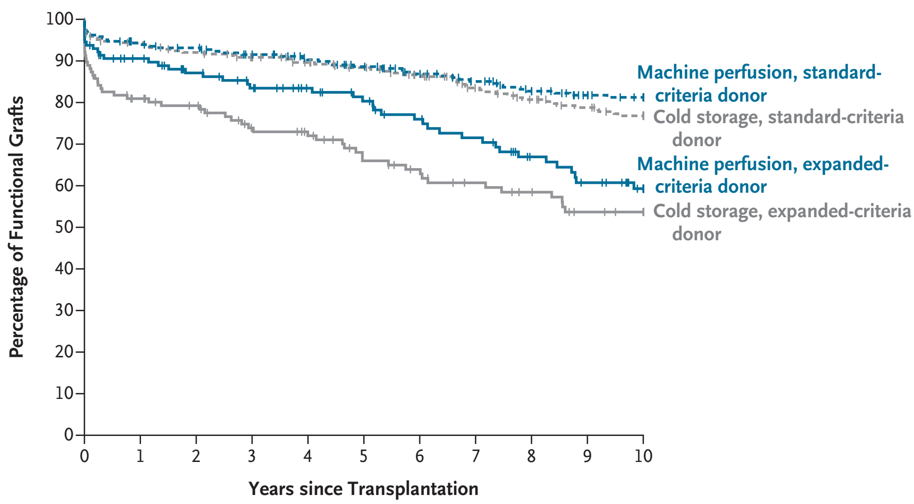
THIS WEEK'S LETTERS

A Graft Survival



No. at Risk											
Machine perfusion	409	366	350	317	299	285	266	250	229	211	197
Cold storage	409	354	340	310	291	273	257	235	221	206	197

B Graft Survival According to Deceased-Donor Subgroup



No. at Risk											
Machine perfusion, standard-criteria donor	271	251	246	226	217	209	197	186	175	163	157
Cold storage, standard-criteria donor	271	252	244	230	216	207	197	181	169	163	156
Machine perfusion, expanded-criteria donor	138	115	104	90	82	76	69	64	54	48	40
Cold storage, expanded-criteria donor	138	102	96	80	74	65	60	54	50	43	41

Figure 1. Graft Survival over 10 Years.

Panel A shows graft survival in 818 patients who received kidney transplants and were included in the combined data for all kidneys obtained from donors after brain death and after circulatory death. Confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing. Panel B shows results from the 818 recipients according to deceased-donor subgroup — standard-criteria donors and expanded-criteria donors (those ≥60 years of age, or 50 to 60 years with compromised renal function or coexisting conditions). All graft survival analyses were performed with data censored at death in patients with a functional graft. No statistical tests were performed on these data.

than from standard-criteria donors, although the limited sample size, the post hoc nature of the analysis, and the lack of adjustment for multiplicity preclude definitive conclusions. In this trial, machine perfusion without oxygenation was provided. A more recent randomized trial showed that oxygenated machine perfusion resulted in better function and graft survival of kidneys from donors 50 years of age or older after circulatory death than nonoxygenated machine perfusion.[5] Oxygenation may therefore further enhance the beneficial effect of machine perfusion.

In this follow-up report involving kidney transplants, the overall graft-survival benefit of machine perfusion over cold storage appeared to remain after 10 years, and patient survival and estimated glomerular filtration rates were similar in the machine-perfusion and cold-storage groups.

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Vepdegestrant in Advanced Breast Cancer

TO THE EDITOR: In their article, Campone et al. (Aug. 7 issue)[1] report that vepdegestrant led to significantly longer progression-free survival than fulvestrant among patients with *ESR1*-mutated advanced breast cancer, whereas no significant difference was observed in the overall population. However, outcomes in the subgroup of patients with *ESR1* wild-type breast cancer remain unreported.

On the basis of published data — and given the proportionality of the Kaplan–Meier curves, which did not cross and support the assumption of constant relative hazards — we calculated an indirect estimation of treatment efficacy in the *ESR1* wild-type subgroup. The results of this analysis suggested that treatment with fulvestrant yields a median duration of progression-free survival of 4.8 months, as compared with 2.7 months with vepdegestrant, which corresponds to an estimated hazard ratio of 1.57 (95% confidence interval [CI], 1.19 to 2.06) in favor of fulvestrant.

This differential efficacy may reflect underlying biologic mechanisms. Wild-type tumors may rely more heavily on ligand-dependent estrogen receptor (ER) signaling, which fulvestrant effectively disrupts. In contrast, emerging preclinical data indicate that resistance to ER-targeting proteolysis-targeting chimeras (PROTACs), including agents such as vepdegestrant, may involve loss of ER expression and activation of mitogen-activated protein kinase and phosphatidylinositol 3-kinase pathways; these characteristics could limit the effectiveness of PROTACs in ER-dependent, *ESR1* wild-type disease.[2]

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No potential conflict of interest relevant to this letter was reported.

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