Supplemental Material

Waiting time for second kidney transplantation and mortality

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1 Emulated trial protocol

Our analysis was based on the emulation of a clinical trial from the observed registry data, a so-called target trial. A real clinical trial for the research question of interest is infeasible due to ethical concerns and the unrealistic logistics of randomizing organ allocation – in contrast to standard medication, donors for kidney transplantation are not available on demand. The general outline of emulating target trials is described e.g. by Hernan and Robins and the references therein.[1] In this section we provide a brief protocol of the pragmatic target trial we emulate in our analysis.

1.1 Target estimands

The primary target estimand is the effect of second kidney transplantation on patient survival in patients who experienced a graft loss after a first kidney transplant. Since this effect is assumed to be different, depending on the time elapsed between graft loss and second transplantation, the secondary target estimand is the effect of second transplantation evaluated at a specific point in time T after graft loss (e.g. at 1 year after first graft loss).

1.2 Eligibility criteria

The trial will include all patients in Austria who experienced a graft loss after a first kidney transplantation and who joined the waiting list for a second kidney transplantation.

Inclusion

- Age older than 18 years
- Graft loss after first transplantation
- On the waiting list for second kidney transplantation between January 1, 1980 and August 31, 2019
- Organ for second transplantation available between January 1, 1980 and August 31, 2019

Exclusion

- Second kidney transplantation not in Austria
- Multi-organ transplantation

1.3 Outcome

The outcome of interest is death from any cause. Patients will be followed from the moment of treatment assignment for a maximum of 15 years, or until death, loss-to-follow-up, or the end of the observation period.

1.4 Treatment strategies

The compared treatment strategies are

- Treatment: Receive a second kidney transplant immediately when it becomes available (under the assumption that for all individuals in the study a fitting donor organ would be available)
- Control: Do not receive a second kidney transplant, now or in the future, and remain on dialysis

1.5 Outcome measures

Survival probabilities for each treatment group up to 15 years of follow-up. Difference in restricted mean survival time (RMST) between the two treatment groups up to 15 years of follow-up. Furthermore, a hazard ratio for mortality comparing the two treatment groups.

1.6 Assignment procedure

Patients will be randomized to the two treatment groups upon joining the study (i.e. when a fitting organ for transplantation becomes available). The study is conducted unblinded.

1.7 Analysis

1.7.1 Primary estimand

The RMST will be estimated by the area under the Kaplan-Meier estimates of the survival curves for each group until 15 years of follow-up. The RMST difference is then computed as the RMST of the transplantation group minus the RMST of the control group. The hazard ratio comparing the two groups will be estimated by a Cox proportional-hazards model for the primary endpoint, using treatment assignment as main exposure.

1.7.2 Secondary estimand

Modification of the effect of transplant by the time after first graft loss at which the transplantation happens will be assessed by RMST differences and hazard ratios derived from a Cox proportional-hazards model including time since first graft loss as an additional covariate, alongside an interaction term with the main exposure.

2 Extended statistical methods

The target estimand of our analysis was the survival benefit of retransplantation compared to remaining waitlisted on dialysis. Although conceptually a causal quantity and analysed by state-of-the-art causal inference methodology, we used the phrase “survival difference” instead of “survival benefit” in this work since the analysis was based on observational data in adherence to CJASN’s publication policies.

Generally, a key issue in assessing the effect of transplantation on survival is the lack of a natural control group in observational data. We addressed this by emulating a series of auxiliary trials mimicking the target trial using the observational registry data and modelling the survival difference of retransplantation and dialysis based on a sequential Cox approach.[2, 3] Whenever a patient in our study received a second transplantation at a time point *T* after their graft loss, an auxiliary trial was started (Supplemental Figure 1). In this auxiliary trial, the treatment group consisted of all individuals who received a transplant at time *T* after their graft loss (possibly more than one individual if multiple transplantations happened at time *T*), and the control group consisted of individuals who had not yet received a transplant, and who were on the waiting list at time *T after their first graft loss*. All further eligibility criteria were also evaluated at the start of the auxiliary trial. The time to the observed outcome for each patient was measured starting from time *T*. The data from all auxiliary trials were stacked and analysed in a single Cox proportional-hazards model using the group assignment as main exposure. In a second model, the time of auxiliary trial start (time between first graft loss and transplantation, *T*) and its interaction with the main exposure were included to model the time-since-graft loss dependent survival difference. Flexible modelling of the starting time using restricted cubic splines was explored, but no relevant departure from linearity was observed, while the inclusion of spline terms increased the variance of the resulting effect estimates. Hence, we preferred simpler linear effects. Each individual may occur multiple times in this analysis, several times as control patient, and a single time starting an auxiliary trial.

Since treatment allocation of the individuals was not randomized in the auxiliary trials, we addressed confounding by using stabilized inverse probability of treatment weights (IPTW), following the approach by Hernan et al.[4] These were obtained as accumulated inverses of the predicted probabilities from a pooled logistic regression models for the group assignment fitted on the stacked dataset. For details see Supplement Section 2.2.

Furthermore, individuals who entered an auxiliary trial in the control group, but were transplanted during the follow-up of that trial were incompatible with the definition of our comparison strategy “remain waitlisted on dialysis and never transplant”. We addressed this “non-adherence” by considering individuals as being censored at the time of their transplantation. This non-random censoring pattern was mitigated by stabilized inverse probability of censoring weights (IPCW) for the control group in each auxiliary trial.[3] The stabilized IPCW were obtained for yearly intervals from Cox proportional-hazards models fitted separately for each trial, for details see Supplement Section 2.3. The outcome for these models was time to transplantation or censoring. For individuals in the treatment group the IPCW were set to unity.

The IPTW and yearly IPCW were multiplied, winsorized at their 0.5% and 99.5% percentiles,

and used in the Cox models on the stacked data as weights. We used 1000 bootstrap resamples of the individuals to provide 95% confidence intervals (CI) for all quantities of interest, computed from the 2.5% and 97.5% percentiles of the bootstrap distributions. In each bootstrap iteration the whole procedure outlined in this section was repeated (data preparation, IPTW, IPCW, final weighted model). Follow-up times were administratively censored at 15 years of follow-up to mitigate the influence of individuals with extremely long observation times, which were not deemed representable. This applied equally to the data for the final model, as well as to each auxiliary trial, in which the follow-up times were counted from the beginning of the trial onwards. We restricted the analysis to auxiliary trials starting within the first 8 years after first graft loss only, due to inadequate sample size for trials starting later. Since the amount of missing data was low we conducted a complete-case analysis, but have considered variables with higher amounts of missingness in the sensitivity analyses outlined in Supplemental Section 4.

2.1 Data preparation

Supplemental Figure 1 summarises the preparation of the observational registry data to provide a dataset which can be used to emulate the target trial as outlined in the statistical methods. Individuals who were removed from the waitlist for any reason were excluded from participation in auxiliary trials from that time onwards. An auxiliary trial was started at each distinct observed transplantation (TP) at a time *T* (time of transplant allocation) after first graft loss. Auxiliary trials in our study were ordered by the time between first graft loss of an individual and transplant allocation. Individuals who received a transplant at time *T* served as experimental group in the trial. Individuals who had joined the waiting list (WL), and had not yet received a transplantation at time *T* in their personal history of follow-up since graft loss were eligible to join the control group of the emulated trial initiated by a TP at time *T*. All further inclusion criteria were also re-evaluated for each auxiliary trial. The outcomes in the auxiliary trials were modified to conform to the definition of the treatment strategies by censoring all individuals from the control group who received a transplant after joining an auxiliary trial, at the time of their transplant. The time to the outcome (death from any cause) for individuals in the trial starting at time *T* was measured from time *T.* For further analysis, the data from all auxiliary trials were stacked into a single dataset.

2.2 Inverse probability of treatment (IPTW) model

IPTW were obtained from a pooled logistic regression models which used the stacked dataset comprising data from all auxiliary target trials following the methodology described by Hernan et al.[4] The outcome of the model was the treatment assignment at the beginning of a trial (retransplantation versus no retransplantation). As covariates the model included the following variables: recipient age at entry to the trial, recipient sex, year of first kidney

transplant, duration of first kidney transplant, duration of dialysis before first transplant, and time between graft loss and initial joining date of the waiting list for the second transplant. To account for the differences between the auxiliary trials, an interaction with time since first graft loss (i.e. starting time of the trial) was added for each covariate. A square-root transformation was applied to time since first graft loss to obtain a more symmetric distribution and improve model fit. In line with Hernan et al,[4] a global intercept for all trials was used. All variables except sex were treated as continuous, and their functional forms were assessed using restricted cubic splines using 4 to 5 knots placed at equally spaced quantiles of the covariates' distributions. The final model was chosen by optimization of the Akaike information criterion (AIC) which balances model fit and model complexity and considerations of the range of the resulting weights. It comprised a 3-knot spline for time between first graft loss and the trial start, the rest of the variables were modelled with linear terms only. The model reached an area under the receiver operating characteristic curve of 0.67.

From this model, probabilities of having received the observed treatment were obtained by the predictions for each observed individual. Assume we wanted to obtain the weight for an individual with covariate vector x participating in auxiliary trial k. First, the probabilities of not having received treatment in all earlier trials were multiplied as $\prod_{i<k} P_i(G = 0|x)$, where G denotes treatment assignment (0 means no retransplantation, 1 means retransplantation). Then, depending on the treatment assignment in trial k, the final factor was either $P_k(G = 1|x)$ if an individual received a transplant, or $P_k(G = 0|x)$ otherwise. The unstabilized IPTW were then obtained as the inverses of these accumulated probabilities.

Stabilizing the IPTW was achieved by estimating the marginal probability of treatment (i.e. second transplantation) per trial, and using the accumulated probabilities as numerator when inverting the unstabilized IPTW. The resulting log-base-2-transformed weights were symmetrically distributed around 0 (i.e. weight 1) with small variance.

2.3 Inverse probability of censoring (IPCW) model

IPCW were obtained from Cox proportional-hazards models fitted separately for each auxiliary trial. These were only used for the control group (remaining waitlisted on dialysis with no retransplantation). For the treatment group the IPCW were set to unity. The outcomes of the models were inverted status indicators for the main outcome, i.e. the event of interest was being censored during the follow-up of an emulated trial due to transplantation or other reasons. The time to the event was measured from the starting time of the auxiliary trial. All observations were administratively censored at 15 years of follow-up after trial start to disregard the effect of long-time observations deemed not representative of the general study population. As covariates the models included the following variables:

recipient age at entry to the trial, recipient sex, year of first kidney transplant, duration of first kidney transplant, duration of dialysis before first transplant, as well as time between graft loss and initial joining date of the waiting list for the second transplant. All variables except sex were treated as continuous and were modelled using linear terms. Further search of functional forms was disregarded due to limited sample sizes in the auxiliary trials, in particular those starting later than a few years of waiting time after first graft loss. From IPCW models, probabilities of remaining uncensored were obtained for each year S of follow-up within an auxiliary trial (e.g. at beginning of the trial $S = 0$, after one year $S = 1$, and so on). The choice to model yearly weights was a compromise between accuracy of the weights, and feasibility of computation – computing weights at every possible observed outcome time for each auxiliary trial would have been prohibitively expensive in terms of computational resources. Smaller interval widths (0.5 years and 0.25 years) did not have an impact on the estimates in a specific sensitivity analysis (data not shown). The unstabilized IPCW were then computed for each individual as the inverses of the probabilities of remaining uncensored at follow-up time S estimated from the Cox model. We stabilized the IPCW by the unadjusted Kaplan-Meier estimate of the probability of remaining uncensored in the numerator.

2.4 Assumptions and limitations of the analysis

There are several assumptions that underlie our analysis approach.

- No unmeasured confounding – we are capturing all variables that confound the association between receiving a transplant and survival. We argue that this assumption holds, due to the use of several variables which act as proxies for other confounders and which allow modeling the general health status of an individual (e.g. time of waitlisting, duration of first transplant and dialysis). Furthermore, we restrict the analysis to individuals on the waiting list with clearly defined entry criteria, thereby ensuring a more homogenous study population compared to simply using all individuals after graft loss.

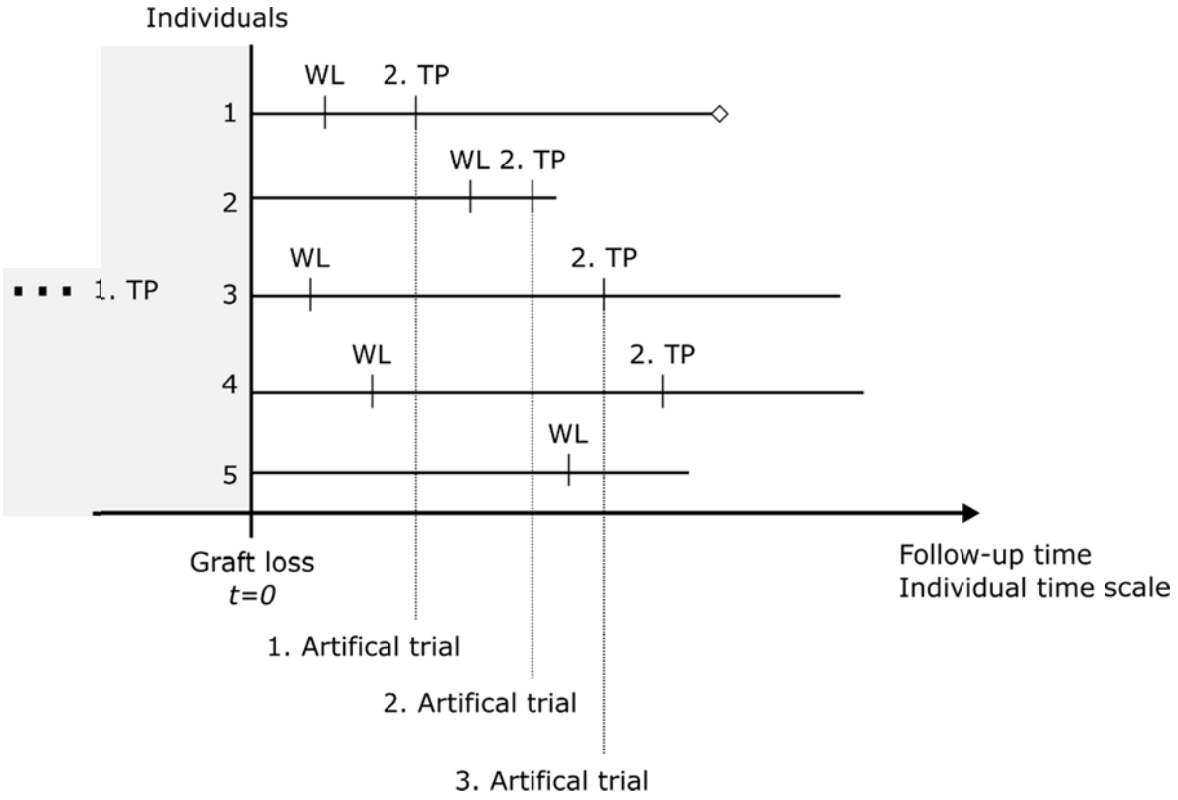
- Among those who received a transplant at time *T*, had they not received a transplant, their survival would have been similar to those on the waitlist at time *T* who did not receive a transplant, all else being equal. Since the fact if, and at which time, an organ from a non-living donor becomes available for transplantation can be considered as being essentially random (i.e. due to extrinsic factors) this is likely to hold.

- Our study assumes that in each emulated target trial, when individuals are compared regarding the effect of transplantation, an ideal graft would have been available for all

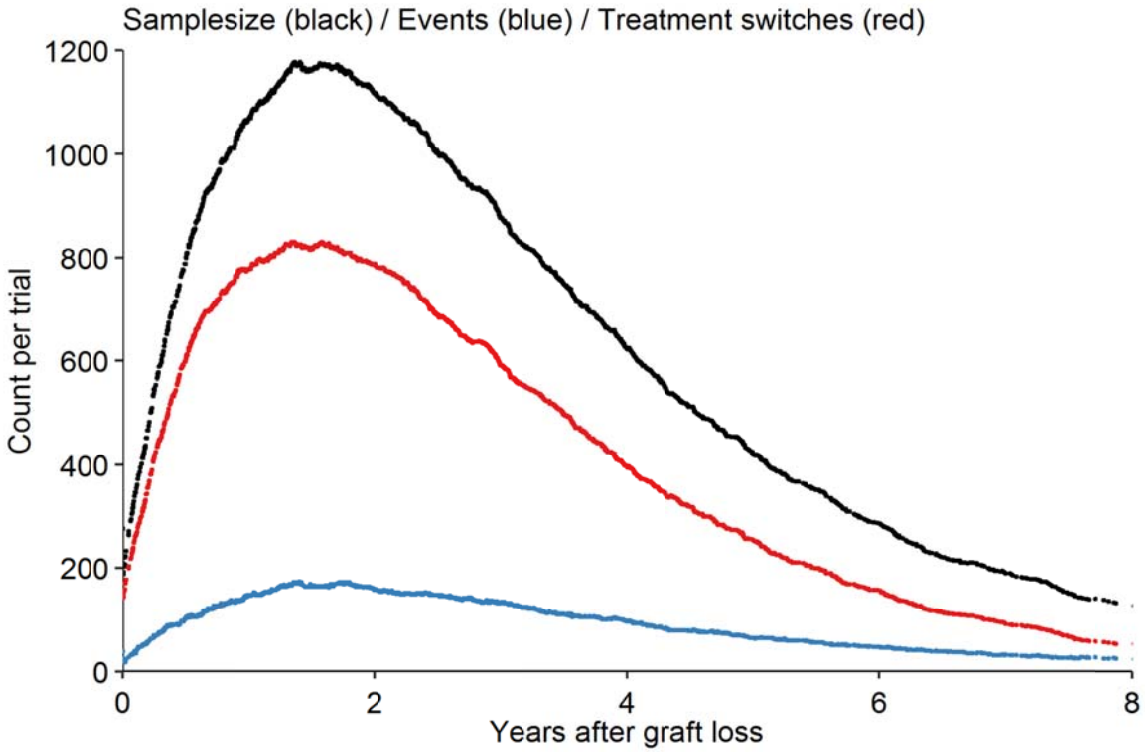
individuals. This is due to the lack of information about the organ allocation lists generated by Eurotransplant matching transplant candidates to available donor organs.

- Our analysis is limited to the Austrian population (i.e. central European, predominantly Caucasian).
- We do not have longitudinally updated information on transplant eligibility, only on the initial entry and removal of the waiting list. We can therefore ensure that individuals deemed unfit for transplantation in the long term were excluded from the analysis as soon as this was diagnosed.

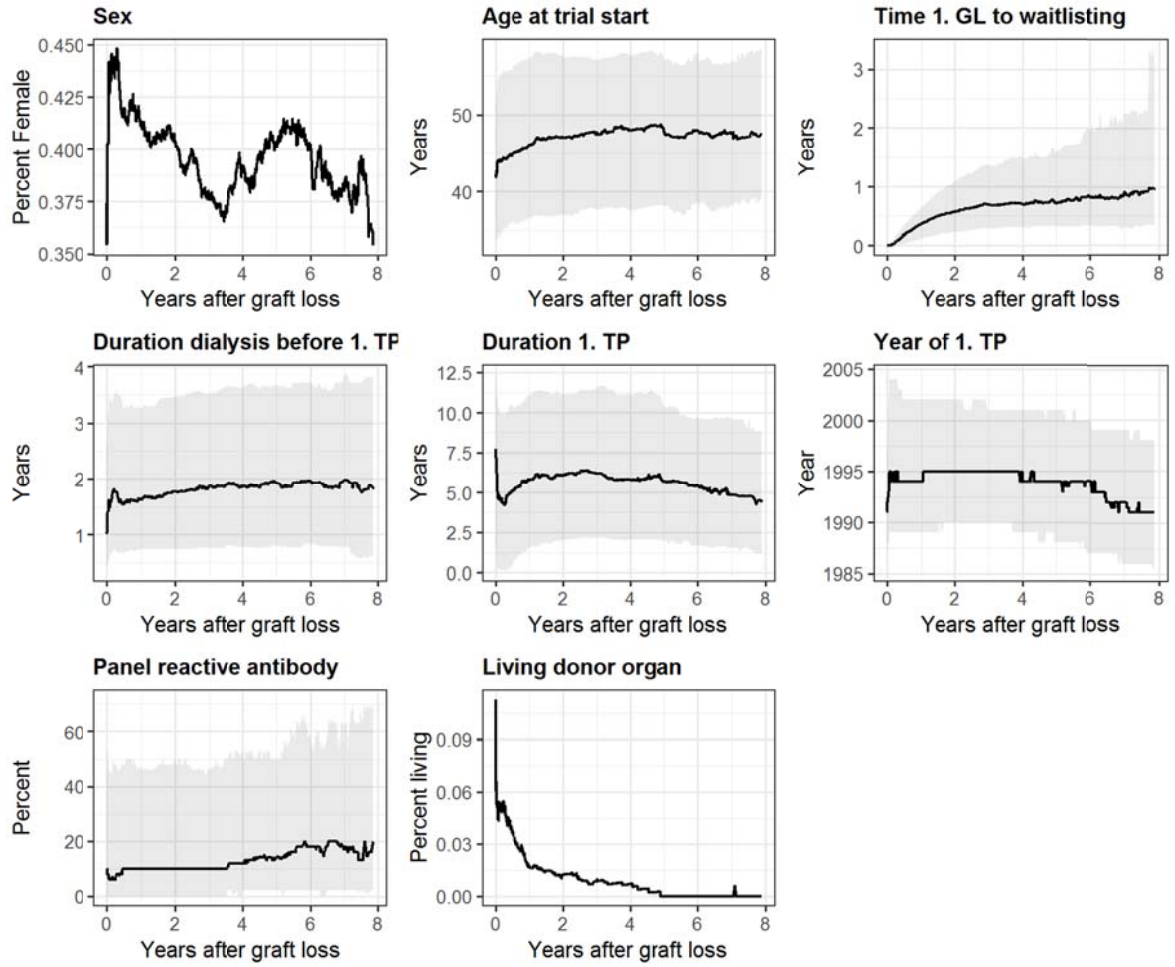
3 Supplemental Figures



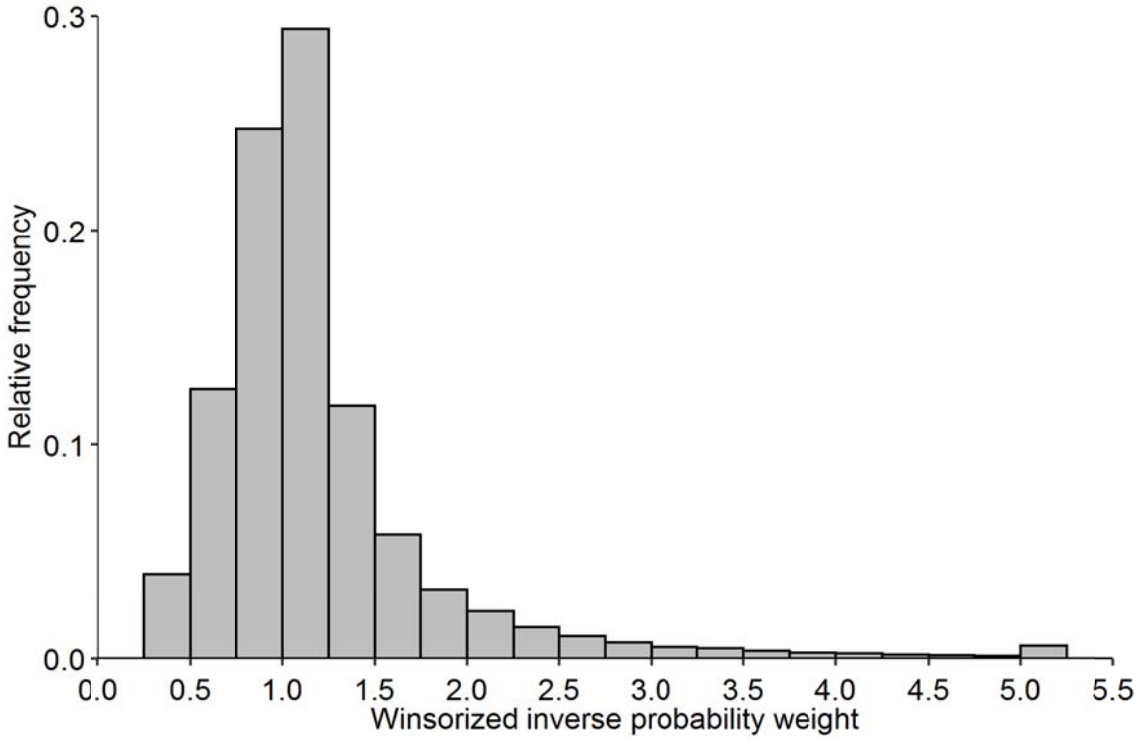
Supplemental Figure 1: Visualisation of study design which defines two main time axes. First, the time axis "time since first graft loss": for each individual the graft loss after first transplantation (1. TP) defines the "baseline", or time 0 (t = 0) of these individual time scales. Second, the time axes defined in each auxiliary trial: auxiliary trials are started at each observed transplantation (TP), representing time 0 for that particular trial, and the time to the outcome is measured from the start of the trial. All auxiliary trials are ordered by the first time axis, i.e. time since graft loss of an individual after the first transplantation. Only individuals who have joined the waiting list (WL), and did not receive a transplantation at that point in their personal history of follow-up since graft loss are eligible to join the auxiliary trial initiated by a TP. Thus, in the graphic above, in the first auxiliary trial starting with the 2. TP of individual 1, individuals 1, 3 and 4 would be eligible, in the second trial started by individual 2, individuals 2, 3 and 4 would be eligible, and in the third trial started by individual 3, individuals 3, 4 and 5 would be eligible. Study outcomes are indicated as filled (death) or empty (survived until date of data lock, loss to follow-up) diamonds. In the first trial, for individuals 1, 3, and 4 the time would be measured from the time of 2.TP of individual 1, to the respective individual outcomes. The outcomes in the auxiliary trials are modified to conform to the definition of the treatment strategies by censoring all individuals who received a transplant after joining an emulated trial at the time of their transplant.



Supplemental Figure 2: Sample size for each auxiliary trial. Each individual may be counted multiple times in this illustration. The black line gives to the total number of individuals entering a single emulated trial. The blue line gives the number of individuals who died during the follow-up of that trial (administratively censored at 15 years after trial start), while the red line gives the number of individuals who started treatment (received a transplant) during follow-up of that trial.



Supplemental Figure 3: Covariate distributions in each auxiliary trial, shown over time since first graft loss. The black lines give relative frequencies for binary variables and median values for continuous ones. The grey area indicates the interquartile range (25th to 75th percentile) of the distribution. “GL” stands for graft loss, “TP” for transplantation. Note that these distributions do not necessarily agree with the cohort characteristics reported in Table 1 of the main manuscript; the latter summarises the whole cohort entering the analysis at first graft loss, while this graphic shows the observed distributions after applying inclusion and exclusion criteria (in particular active waitlist status) in each auxiliary trial at specific time points after first graft loss. This represents the changing population characteristics conditioned on in the analysis over time. Apart from slight discrepancies in the first few months after graft loss (partly also attributable to small sample sizes in these auxiliary trials), most cohort characteristics stay comparable (also to Table 1) over the study period. Exceptions include age at trial start (which increases with time, as expected from the definition), time between first graft loss and waitlisting for second transplantation (which increases with time, as to be expected from the definition), and receipt of a living donor organ (the longer the waiting time the less likely it is to receive a living donor organ).



Supplemental Figure 4: Histogram of relative frequencies of inverse probability weights used as observations weights in the final Cox analysis models. These weights were computed as the product of stabilized inverse probability of treatment weights trial to address confounding, and yearly stabilized inverse probability of censoring weights to address adherence to the treatment strategies of interest. The final weights were winsorized at their 0.5% and 99.5% percentiles to remove outliers with highly impactful weights.

4 Sensitivity analyses

A number of sensitivity analyses were conducted to assess the robustness of the main results regarding decisions made for the modelling process or subgroups of the data, and to explore differences in the magnitude of the estimated effects in different subgroups. Thereby we provide additional insights into how patient characteristics changing over time impact the results.

For individuals with missing waitlist date, but who underwent a second transplantation, the waitlist date was set to the date of transplantation. This is a simple way to impute the value and can be considered conservative, as these individuals do not play a role in any auxiliary trial other than when they were transplanted themselves. Furthermore, since we thoroughly attempted to obtain all such data, the missingness of the waitlist date is most likely at random, and no clear reasons were found why individuals did not have a waitlist date. Nevertheless, we also considered a “complete case” analysis which excluded these individuals (n = 265) from all computations (IPTW, IPCW, final analysis model).

The proportional hazards assumption for the main Cox model was assessed using stratification per treatment group in the stacked dataset comprising the data from all auxiliary trials. It is known that transplantation increases the short term hazard for mortality within the first few months. Our main model ignored this and assumed the same baseline hazard for both treatment groups, which may be problematic for the comparison of short term survival differences. While this was not the focus of our study, we nevertheless assessed the impact on the results when separate baseline hazards were fitted based on the treatment assignment in each auxiliary trial. Furthermore, the use of stratification precludes the estimation of an effect estimate for the group factor (i.e. a hazard ratio), which is why we did not report it as main analysis.

The proportional hazards assumption of the IPCW models was assessed using Aalen additive hazards models for the estimation of the denominator probabilities, which allowed a much more flexible modelling of the time-to-event outcome. These were fitted using the same data as the IPCW Cox models in each auxiliary trial separately, with the same variables and no assumptions regarding their functional forms. The additive hazards models were implemented using the R package timereg 1.9.6.[5]

The impact on the results of the inclusion of immunological sensitization as measured by panel reactive antibodies (PRA) was assessed by including PRA as a covariate in the IPTW and IPCW models and fitting the final Cox model as outlined in the main manuscript. The reason PRA was not included in the main analysis was the high amount of missing data, as reported in Table 1 (17% missing values). The use of multiple imputation was considered,

but disregarded due to the high computational demand, in particular because of bootstrap based inference.

The impact of donor type on the effect of second transplantation was assessed by re-doing the analysis (IPTW, IPCW and main models) excluding transplantations from live donors. It is known that the population characteristics of recipients of transplantations from live donors may differ from those receiving transplantations from deceased donors. Our study data comprised 5% of living donor transplantations.

The analysis used data spanning multiple decades during which transplantation practice has changed over time. To reflect this, we re-did the analysis excluding all patient data from before 1994, the year in which immunosuppression markedly changed in the Eurotransplant region and after which no major differences compared to current transplant practice are to be expected. Thus, this analysis only includes data from individuals with first graft failure after 1994, or who were on the waiting list for a second transplantation after 1994.

A check of the impact of high observation weights on the main Cox model was conducted by decreasing the horizon for administrative censoring of follow-up to 10 years, instead of 15 years. This included the computation of the IPCW as well as the main model.

4.1 Results

Results from the sensitivity analyses are summarised in Supplemental Table 1. All sensitivity analyses showed general agreement with the results reported in the main manuscript and provide further insights on the effect of retransplantation. Of interest is the larger effect size of second transplantation in the analysis on individuals with complete waitlist data only. Similarly, restricting the analysis to individuals with available PRA measurements showed a larger effect of retransplantation, but also larger variability due to the exclusion of individuals. Stratification by the treatment strategy demonstrated that the known short term increased risk of death due to transplantation does not impact RMST differences negatively beyond 5 years of follow-up. Results for alternative IPCW (Aalen) showed higher variability compared to the main analysis, but the results are in good agreement indicating no issues with the proportionality assumption for the IPCW models. The effect of retransplantation in recipients of organs from deceased donors was less pronounced compared to the overall population, as this subgroup usually has to wait longer for available organs than if a live donor is available. In an analysis excluding data prior to 1994, we observed a larger effect of retransplantation than in the main analysis. This is likely attributable to the changes in transplantation procedures and medical care over time and may be relevant for the interpretation of the results regarding future transplantation practice.

Results for sensitivity analyses for the effect of transplantation at different times after first graft loss provided a similar, positive assessment regarding robustness and led to the same conclusions as the main analysis (results not shown for brevity).

Supplemental Table 1: Summary of results for effect of second transplantation for all sensitivity analyses. CI denotes confidence interval.

Analysis	**Hazard ratio (95% CI)**	**Difference in restricted mean survival time In months (95% CI)**	
		At 5 years	**At 10 years**
Main	0.73 (0.53 to 0.95)	1.6 (0.3 to 2.9)	5.8 (0.9 to 11.1)
Only complete waitlistdata[1)]	0.56 (0.43 to 0.76)	2.7 (1.4 to 3.9)	10.5 (5.1 to 15.5)
Stratified by treatment strategy[2)]	-	1.6 (0.1 to 3.1)	8.2 (3.4 to 12.6)
Alternative IPCW (Aalen)	0.74 (0.57 to 1.01)	1.5 (-0.1 to 2.7)	5.4 (-0.2 to 10.1)
Including PRA[3)]	0.58 (0.38 to 0.91)	2.3 (0.5 to 3.7)	9.2 (1.8 to 15.5)
Excluding live donor transplantations[4)]	0.81 (0.60 to 1.08)	1.1 (-0.4 to 2.5)	3.9 (-1.4 to 9.3)
Excluding data prior to 1994[5)]	0.47 (0.35 to 0.64)	3.8 (2.3 to 4.9)	14.5 (8.7 to 19.7)
Alternative censoring horizon[6)]	0.61 (0.47 to 0.83)	2.3 (0.9 to 3.4)	-

1) Excluding 265 (8.9% of whole dataset) individuals without complete waitlist data.

2) No hazard ratio estimate available due to stratification.

3) Excluding 407 (17.5% of whole dataset) individuals without information on PRA.

4) Excluding 115 (5% of whole dataset) individuals with organ from live donor

5) Including 984 auxiliary trials (66% of analysis) and 1836 individuals (78% of whole dataset)

6) Due to the administrative censoring horizon at 10 years, results for RMST at 10 years are not available.

5 References

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