Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: van Rijn R, Schurink IJ, de Vries Y, et al. Hypothermic machine perfusion in liver transplantation — a randomized trial. N Engl J Med 2021;384:1391-401. DOI: 10.1056/NEJMoa2031532

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List of Investigators and Study Sites

The DHOPE-DCD trial was investigator-initiated and designed as a multicenter, prospective, two-group, randomized, controlled, clinical trial and carried out in six liver transplant centers in The Netherlands, Belgium and the UK: **University Medical Center Groningen** in Groningen, **Erasmus University Medical Center** in Rotterdam, **Leiden University Medical Center** in Leiden, The Netherlands; **University Hospitals of Leuven** in Leuven and **Ghent University Hospital** in Ghent, Belgium; and **Kings College Hospital NHS Foundation Trust**, in London, United Kingdom.

The trial was coordinated by the University Medical Center Groningen in The Netherlands, the trial sponsor. The following persons participated in the DHOPE-DCD trial:

Coordinating Investigator/Project Leader:
Robert J. Porte
General Trial Coordinator:
Rianne van Rijn
Assistant Trial Coordinators:
Yvonne de Vries, Otto B. van Leeuwen, Martijn P.D. Haring
Writing Committee:
Rianne van Rijn, Jeroen de Jonge, Aad P. van den Berg, Bart van Hoek, Robert J. Porte
Data and Safety Management Board:
Eric A.M. Verschuuren, Mostafa El Moumni, Cyril Moers
Trial Monitors:
Liza Lahaye, Jan Bottema
Adjudication Committee:
Robbert J. de Haas, Jules J.G. Slangen, François E.J.A. Willemssen

Local Investigators Per Site

Study Site	Principle Investigator	Associate Investigators	Research Coordinators	Organ Perfusionists
Groningen	Robert Porte	Marieke de Boer, Ruben de Kleine, Carlijn Buis, Vincent de Meijer, Joost Klaase, Maarten Nijkamp, Frederik Hoogwater, Aad van den Berg	Rianne van Rijn, Yvonne de Vries, Otto van Leeuwen, Martijn Haring, Jan Bottema	Alix Matton, Laura Burlage, Gert-Jan Pelgrim, Leonie Venema, Rinse Ubbink, Yvonne de Vries, Otto van Leeuwen, Martijn Haring
Rotterdam	Jeroen de Jonge	Wojciech Polak, Sarwa Darwish Murad, Jan IJzermans, Herold Metselaar	Ivo Schurink	Ivo Schurink, Sjoerd van den Hoek, Nemo Backx, Dimitri Sneiders, Özgür Eryigit, Stef Luimes, Femke de Goeij
Leiden	Bart van Hoek	Joris Erdmann*, Volkert Huurman, Ian Alwayn	Babs de Klerk	Jason Doppenberg, Asel Arykbaeva, Lex Habets, Fenna van de Leemkolk
Leuven	Diethard Monbaliu	Ina Jochmans, Nicholas Gilbo, Jacques Pirenne, Maurico Sainz-Barriga	Sarah Mertens, Linde Besard, Sofie Vets	Karlien Degezelle, Lieven Lenaerts, Kristof Van de Voorde, Frederik Gaublomme
Ghent	Roberto Troisi†, Aude Vanlander	Xavier Rogiers‡	Kathleen Segers, Betsy van Loo	
London	Nigel Heaton	Miriam Cortes Cerisuelo	Melissa Preziosi, Anastazja Mroz, Vernie Ramalingham, Jo Gambell, Ane Zamalloa	Mona Dave, Augustine Joseph, Merve Surucu

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‡ Xavier Rogiers passed away on November 20, 2019.

Funding and Support

Fonds NutsOhra (Amsterdam, the Netherlands) supported the DHOPE-DCD trial with a grant for applied medical research (Nr. 1404-012). Bridge-to-Life Ltd. (Northbrook, IL, USA) supported the trial by providing machine perfusion fluid (Belzer MPS UW machine perfusion solution) free of charge. Each participating center covered the costs for the purchase of a machine perfusion device and training of perfusionists was provided by the manufacturer (Organ Assist B.V., Groningen, the Netherlands) as part of their regular after-sales responsibilities. The supporting organizations had no role in the study design, collection, management, analysis, interpretation of data, writing of the report, or decision to submit the report for publication.

Supplementary Methods

Study oversight

The trial was registered before recruitment at Clinicaltrials.gov with identifier NCT02584283 and published in a peer-reviewed journal.[1] The protocol was approved by research ethics committees at each trial site and medical device regulatory bodies in each country, in particular the Inspectie Gezondheidszorg en Jeugd (IGJ) in the Netherlands, the Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten (FAGG) in Belgium and the London-Dulwich National Research Ethics Committee (NREC) and Medicines and Healthcare Regulatory Agency (MHRA) in the UK. The trial was conducted according to the guidelines of Good Clinical Practice and the principles of the Declaration of Helsinki.

Statistics

Additional background information on sample size calculation

The study was powered to detect a clinically relevant difference in incidence of non-anastomotic biliary strictures (NAS) between the two study groups. The incidence of NAS is 29% after donation after circulatory death (DCD) liver transplantation and is 11% after donation after brain death (DBD) liver transplantation in patients transplanted in the University Medical Center Groningen from 2008 to 2013 (unpublished data). This is similar to incidence reported by Abt, et al (27% in DCD versus 2% in DBD transplantation), Dubbeld, et al (24% versus 8%), Croome, et al (22% versus 4%, and Meurisse, et al (33% versus 12%).[2-5] With the intervention (hypothermic oxygenated machine perfusion; DHOPE) we aimed to reduce the incidence of NAS after DCD liver transplantation to the level observed after DBD liver transplantation (proportional reduction of 60%; absolute difference of 29-11=18%). We based this presumed reduction on our results in the pilot study in which 1 of 10 (10%) of the patients with a machine perfused treated liver developed NAS.[6] The other previously reported pilot studies observed no NAS in

any of the patients receiving a DCD liver treated with end-ischemic hypothermic oxygenated machine perfusion.[7,8]

Organ procurement

All livers were retrieved, preserved and transported to the transplant centers according to standard practice, using conventional static cold preservation. The only deviation from regular procurement practice was that the procuring teams were requested to leave a segment of 3-5 cm circular supratruncal aorta attached to the coeliac trunk, if possible. The cystic duct was ligated and the bile ducts were flushed with preservation fluid. The gallbladder was preferably not removed. Donor in situ cold aortic perfusion during procurement was performed using standard preservation fluid, preferably with University of Wisconsin cold storage solution. After procurement the liver was additionally flushed via the portal vein with at least 1 liter of preservation fluid until venous effluent was clear.

Machine perfusion device

Simultaneously with the back table procedure, the Liver Assist (LA) was prepared for use. The LA is a dedicated machine for ex-vivo liver perfusion during storage. It is a CE marked device (European Union Certification of Safety, Health and Environmental Requirements) that is designed, produced, and delivered by Organ Assist (Groningen, The Netherlands). The LA enables dual perfusion via the portal vein and the hepatic artery using two centrifugal pumps to provide a continuous venous flow and a pulsatile arterial flow at 60 bpm. The system is pressure controlled which allows autoregulation of the flow through the liver, with constant pressure at variable flow rates (Figure). For the present trial, the disposable set of LA was filled with 4 L cold UW MP with additional 3 mmol/L glutathione (Biomedica, Foscama Group, Roma, Italy). The perfusion pressure was set to a mean of 25 mmHg for the hepatic artery and 5 mm Hg for the portal vein. These pressure settings are based on previous studies and are lower than physiological pressures to avoid shear stress of the cold endothelium of the hepatic vasculature.[6,9,10] The temperature of the perfusion fluid was set to 10°C. The oxygen flow was set to 500 mL/min of 100% oxygen on each of the two membrane oxygenators. This flow is adequate to obtain a pO2 (>100 kPa or > 750 mmHg) which has been reported to be effective in increasing hepatic adenosine tri-phosphate (ATP) and not harmful to the graft.[10-12]

Prior to machine perfusion, the portal vein and aortic root to the artery of the donor liver were cannulated using 25 Fr cannulas (Organ Assist). Shortly before connection to the device, livers were flushed via the portal vein with 1 L cold (0-4°C) machine perfusion solution to remove cold storage solution. The evolution of arterial and hepatic flows and vascular resistance during machine perfusion are depicted in Fig. S4.

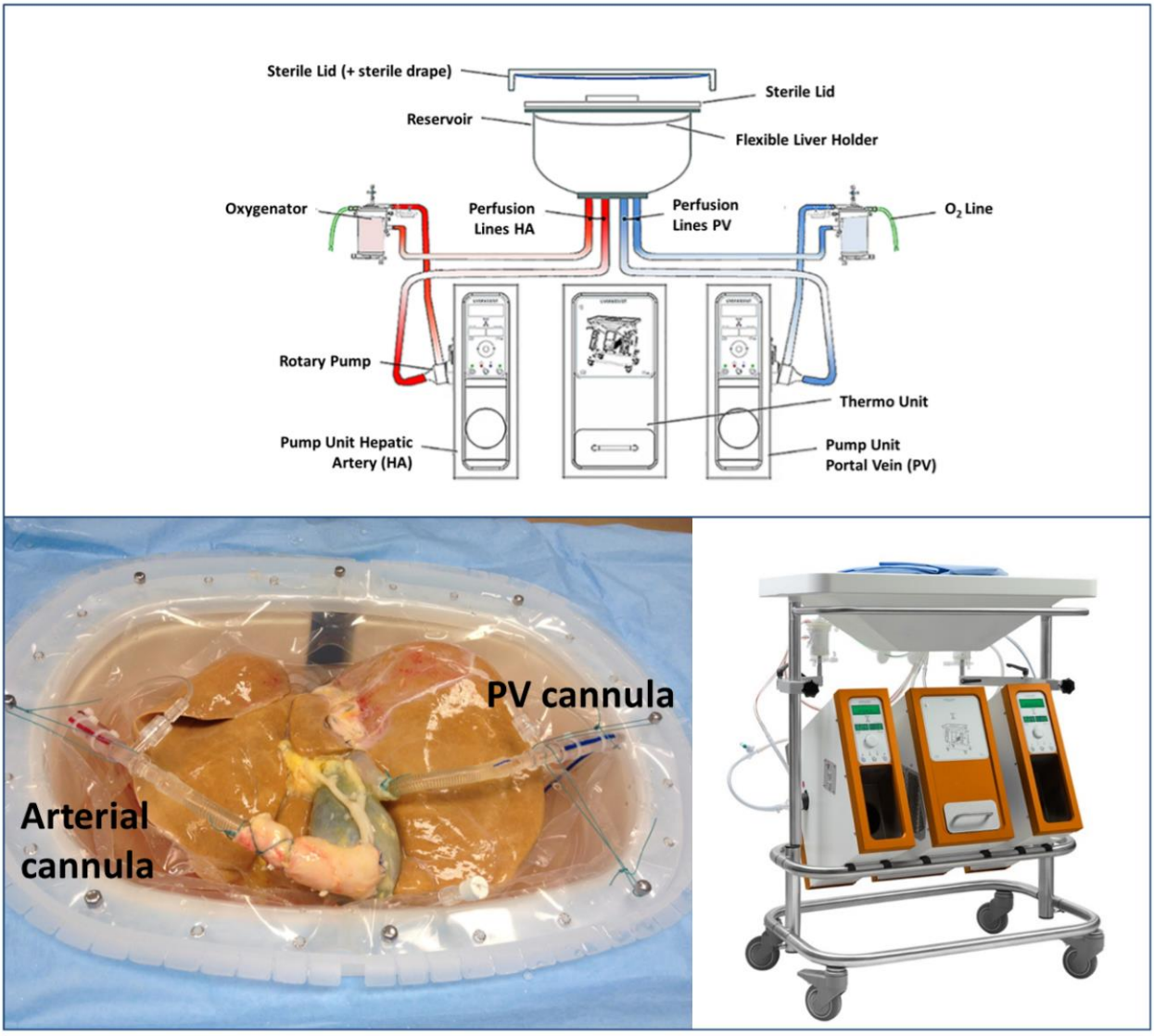

Figure. Details of the Liver Assist and perfusion set up. PV, portal vein; HA, hepatic artery.

Assessment and reporting of study outcome

Outcome measures and serious adverse events were collected and reported by local principle investigators using the secured online software package OpenClinica (OpenClinica, LLC, Waltham, MA, USA), an electronic data capture and management platform (www.openclinica.nl).

The data were first retrieved from OpenClinica for analysis on June 25, 2020. The final database is held by the trial team, which collected the data from trial sites and performed analyses at the Department of Surgery, University Medical Center Groningen.

Biological samples from each liver and recipient were collected and stored in a biobank, for use in further mechanistic studies.

Role of the data safety monitoring board

The roles and responsibilities of the independent data safety monitoring board (DSMB) for the DHOPE-DCD trial were described in the DSMB Charter, including the timing of meetings, methods of providing information to and from the DSMB, frequency and format of meetings, statistical issues and relationships with other committees. As specified in the study protocol, the DSMB performed regular interim analyses on adverse events, to timely detect any safety concerns. The trial could be stopped early due to unacceptable safety concerns (the analysis had to reveal significant (serious) adverse events in the treatment group compared to the control group), or in case new external information would arise that convincingly answered the study question or raised serious safety issues. No interim analyses of study end points were carried out unless there were concerns about the safety of machine perfusion based on the incidence of adverse events. In that case, the Pocock sequential boundary would be used to determine statistical significance of adverse events between the two groups, dictating a Z-value of 2 and thus a P-value of 0.045. No safety concerns were raised by the data safety monitoring board during study progress or thereafter.

Monitoring and quality assurance

Certified monitors collaborating with the Trial Coordinating Center of the Department of Epidemiology, University Medical Center Groningen and with the trial sites performed regular monitoring visits at the trial sites (www.tcc.umcg.nl). The monitoring reports were sent to the trial coordinator and principle investigator.

Supplementary Results

Cholangiography

To ensure correct reporting of all cases of non-anastomotic biliary strictures by the local investigators, a trial magnetic resonance cholangiography was performed at 6 months after transplantation in patients who were not already clinically diagnosed with non-anastomotic biliary strictures. In all 19 patients who developed symptomatic non-anastomotic biliary strictures, the diagnosis was made prior to the trial magnetic resonance cholangiography at 6 months post-transplant. The trial cholangiographies, as well as all clinical cholangiographies performed in symptomatic patients, were available for blinded review.

Ten patients had died or were retransplanted without signs of non-anastomotic biliary strictures prior to the 6-months protocol cholangiography. In addition, protocol magnetic resonance cholangiography was not performed in one patient because of poor condition due to disseminated hepatocellular carcinoma and in five patients due to an omission (Details in Fig S1 and Table S3).

This resulted in a total 140 post-transplant cholangiographies for blinded review. In 7 cases, the images were judged to be of insufficient quality, resulting in a total of 133 cholangiographies that could be analyzed. This included 19 clinical cholangiographies that were performed in patients with symptomatic non-anastomotic biliary strictures within 6 months after transplantation.

Overall, non-anastomotic biliary abnormalities were noted in 93 of these 133 (70%) cholangiographies, of which 74 were in 114 (65%) asymptomatic patients. Radiological evidence of biliary pathology was confirmed for all 19 patients with symptomatic non-anastomotic biliary strictures (Table S4). For those patients who were not reported as having clinical evidence of non-anastomotic biliary strictures, but did have biliary abnormalities on the protocol cholangiography at 6-months, we have checked whether the laboratory tests at 6-months revealed evidence of cholestasis and whether or not this could be explained by another reported complication, such as graft rejection or an anastomotic biliary stricture. This quality check did not reveal any patient with the suspicion of symptomatic non-anastomotic biliary strictures, who was not reported by the local investigators. A comparison of cholestatic laboratory variables in patients with symptomatic and asymptomatic biliary strictures is presented in Table S5.

The radiological severity of cholangiopathy was graded based on a grading system as previously describe by Buis, et al.[13] According to this grading system, the severity of biliary strictures was categorized as mild, moderate or severe, depending on the total number of strictures, the degree of narrowing, prestenotic dilatation, and mucosal irregularity, and finally the extensiveness of the strictures. The radiological severity of cholangiopathy was more severe in symptomatic vs. asymptomatic patients (Table S6). There were no differences in asymptomatic radiological cholangiopathy between the machine perfusion group and control group (Table S7).

These finding are in line with previous reports on the accuracy of magnetic resonance cholangiography in the detection of non-anastomotic biliary strictures after liver transplantation. While the reported

sensitivity varies between 91% and 100%, specificity has been reported as low as 50%.[14] The high rate of radiological biliary abnormalities detected in otherwise asymptomatic patients is an interesting finding that necessitates further research as to why many radiological biliary irregularities apparently remain clinically irrelevant.

Supplementary Figures

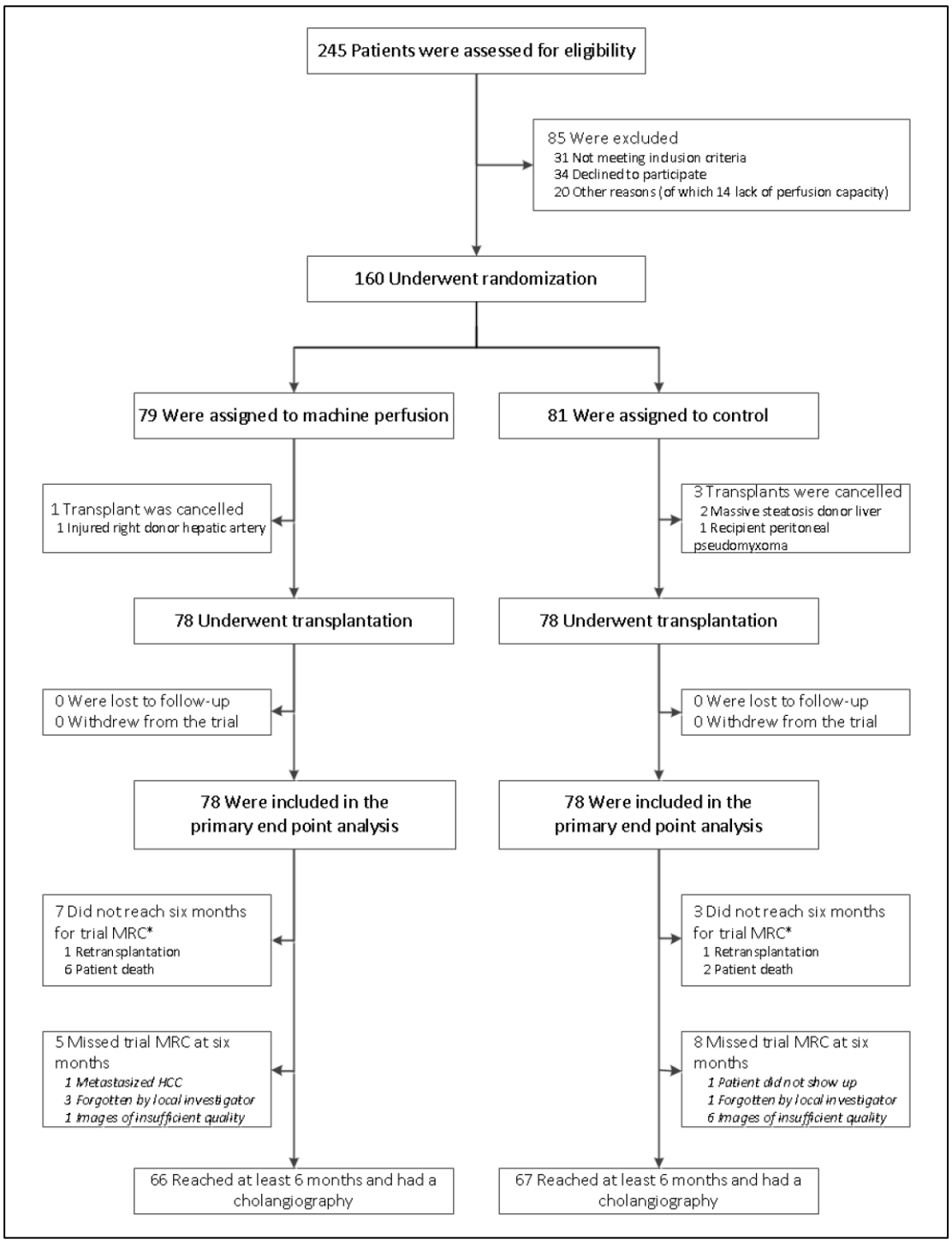

Figure S1. Flow Diagram of Patient Enrollment, Randomization and Follow-up.

* Death or retransplantation not related to non-anastomotic biliary strictures.

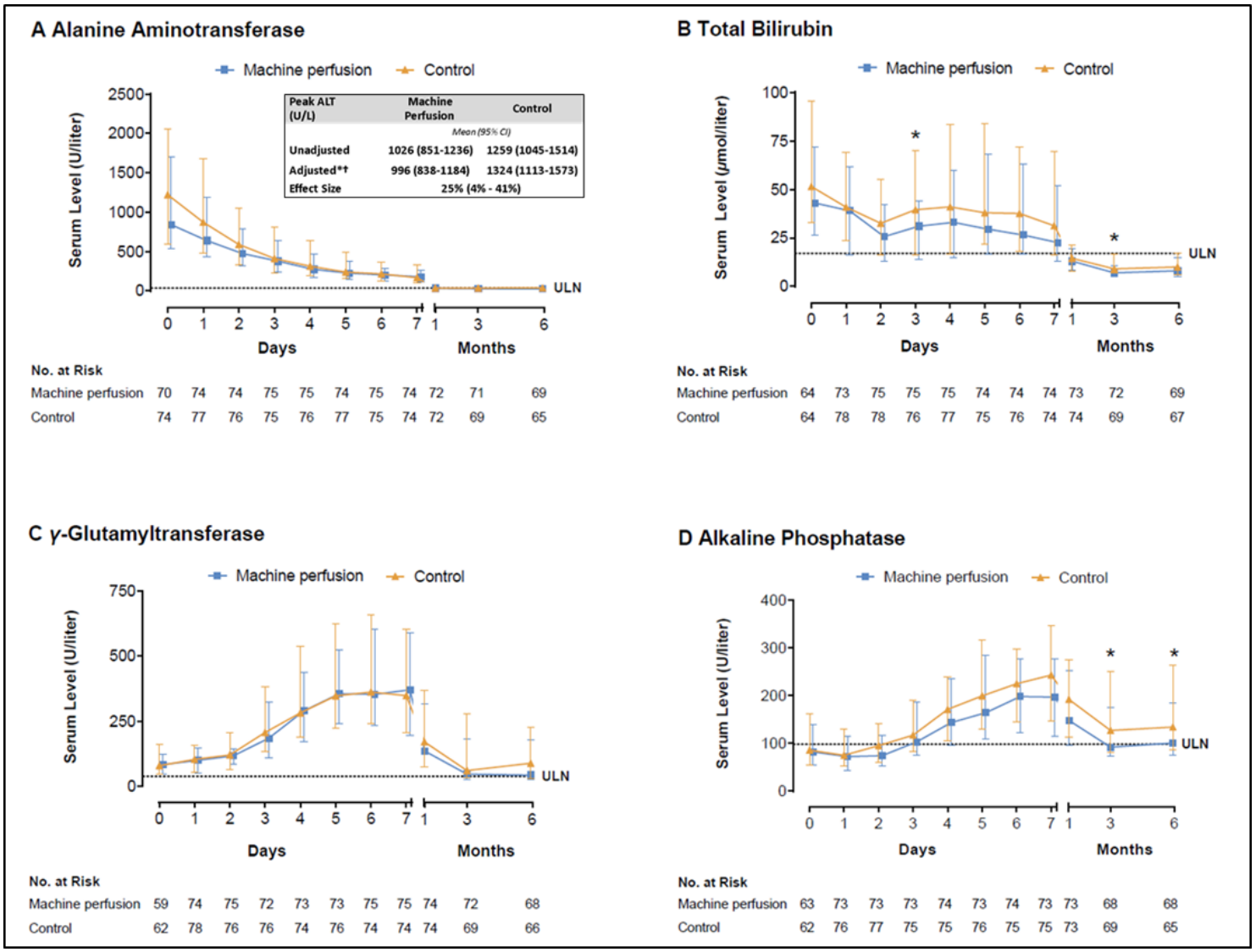

Figure S2. Laboratory Analyses of Serum Liver Function and Injury Tests.

Data presented are median and interquartile range. To convert results for serum bilirubin from µmol/L to mg/dL, divide results by 17.1. ULN denotes upper limit of normal. * $P < 0.05$. There was no adjustment for multiplicity and these analyses should be considered exploratory.

† Peak geometric mean serum alanine aminotransferase (ALT) was calculated after log transformation and correction for trial center, donor body mass index and donor risk index.

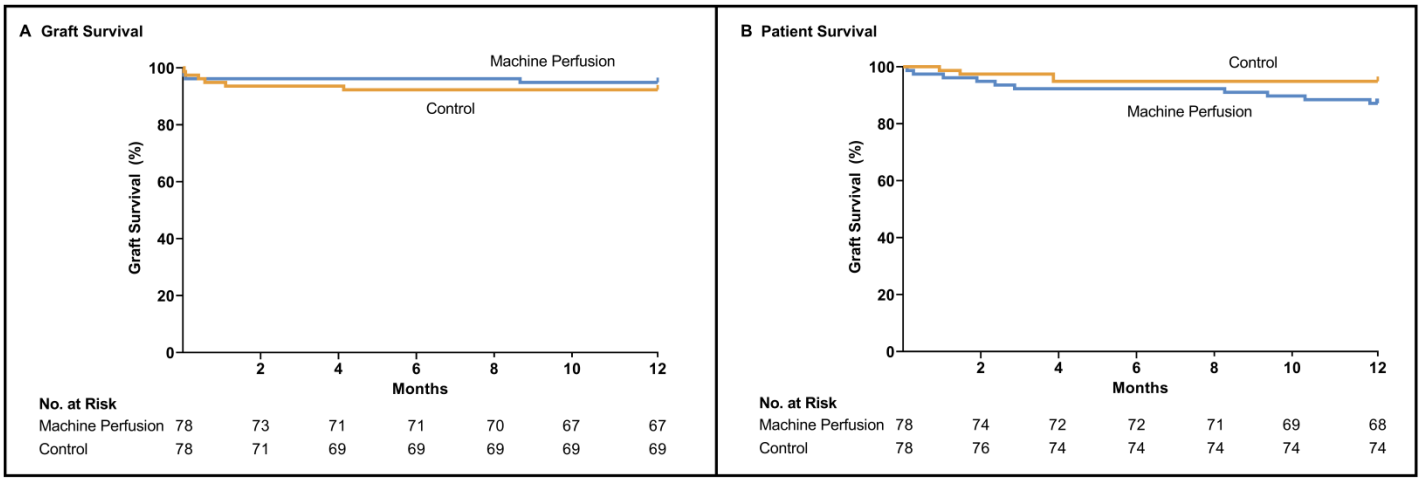

Fig S3. Kaplan–Meier Curves of Graft and Patient Survival after Transplantation.

Panel A shows the Kaplan–Meier curve of graft survival, with censoring of data for patients who died with a functioning graft. Panel B shows the Kaplan–Meier curve of patient survival. Hazard ratio for graft survival 0.65 (95% CI, 0.18 – 2.29) and for patient survival 2.45 (95% CI, 0.77 – 7.85)

Flow Characteristics During Hypothermic Oxygenated Machine Perfusion

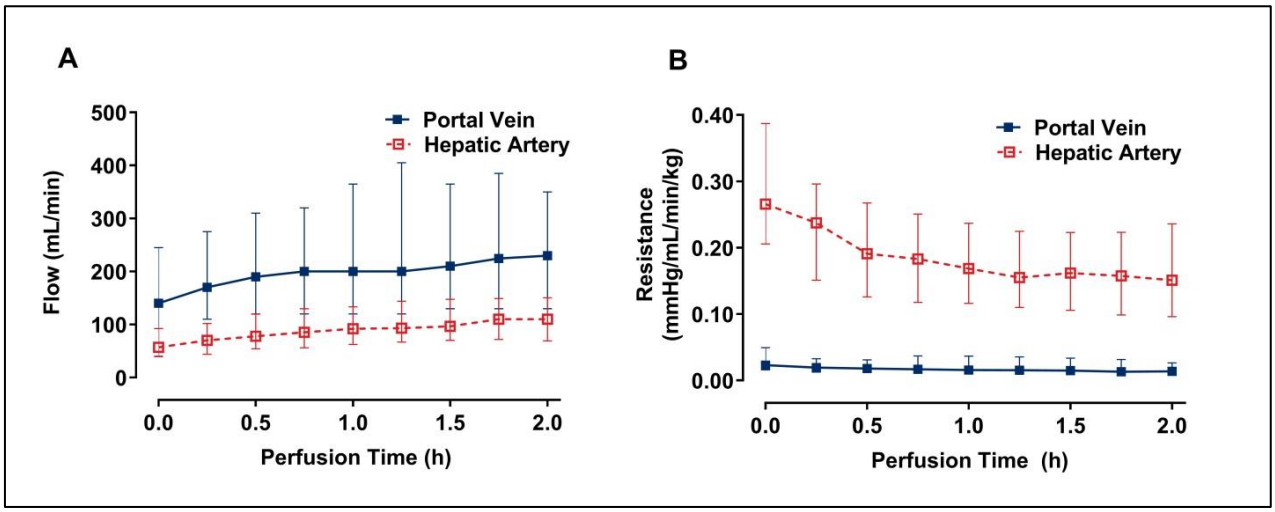

Figure S4. Perfusion Flows and Resistance During *Ex situ* Hypothermic Oxygenated Machine Perfusion.

Data are presented as median and interquartile range.

Supplementary Tables

Table S1. Characteristics of the Donors and Recipients at Baseline.*		
Variable	**Machine Perfusion (N=78)**	**Control (N=78)**
Donor characteristics		
Age – yr	52 (43-57)	49 (37-59)
Male sex – no. (%)	52 (67)	51 (65%)
Cause of death – no. (%)		
Cerebrovascular accident	18 (23)	18 (23)
Post-anoxic brain injury	23 (30)	31 (40)
Trauma	18 (23)	17 (22)
Miscellaneous†	19 (24)	12 (15)
Donor risk index‡	2.12 (1.84-2.38)	2.12 (1.86-2.42)
Body mass index – kg/m^2	25 (23-27)	25 (21-28)
Preservation characteristics		
Time from withdrawal of life support to aortic flush-out – min	29 (22-33)	27 (21-35)
Time from donor circulatory arrest to aortic flush-out – min	11 (8-13)	11 (8-15)
Static cold ischemia time§ – h:min	6:11 (5:16-6:55)	6:49 (5:56-7:57)
Machine perfusion time – h:min	2:12 (2:00-2:33)	NA
Total preservation time¶ – h:min	8:44 (7:46-9:16)	6:49 (5:56-7:57)
Recipient characteristics		
Age – yr	60 (52-65)	60 (52-65)
Male sex – no. (%)	55 (71)	52 (67)
Indication for transplantation		
Cryptogenic liver cirrhosis	4 (5)	1 (1)
Hepatitis B/C	4 (5)	3 (4)
Hepatocellular carcinoma	12 (15)	12 (15)
Metabolic liver disease	3 (4)	3 (4)

Non-alcoholic steatohepatitis	12 (15)	9 (12)
Post-alcoholic liver cirrhosis	19 (24)	22 (28)
Primary biliary cholangitis	5 (6)	8 (10)
Primary sclerosing cholangitis	9 (12)	13 (17)
Polycystic liver disease	3 (4)	0
Retransplantation	3 (4)	5 (6)
Miscellaneous**	4 (5)	2 (3)
Laboratory MELD score	14 (10-19)	16 (10-22)
Renal replacement therapy	3 (4)	2 (3)

***** Continuous data are presented as median and interquartile range (IQR). NA denotes not applicable, MELD, model of end-stage liver disease.

† Donor cause of death in the machine perfusion group was euthanasia in 14 donors, hemorrhage not specified in 1, bacterial meningitis in 1, brain tumor in 1, respirational not specified in 1, and circulatory not specified in 1 donor. In the control group, donor cause of death was euthanasia in 7, suicide not specified in 3, and bacterial meningitis in 2 donors. Results of DCD liver transplantation after euthanasia in the Netherlands and Belgium are similar to those after transplantation of other types of controlled DCD livers.[15]

‡ Donor risk index is a scoring system developed to quantitatively predict the risk of post-transplant graft failure in liver transplantation, based on donor risk factors.

§ Defined as time between aortic cold flush-out in donor to reperfusion in recipient minus machine perfusion time.

¶ Defined as time between aortic cold flush-out in donor to reperfusion in recipient. P value <0.001 for comparison of the two groups.

**Miscellaneous indications for liver transplantation in the machine perfusion group were Morbus Rendu-Osler-Weber in 1, non-cirrhotic portal hypertension in 1, congenital liver fibrosis in 1, and Morbus Caroli in 1 patient. In the control group, miscellaneous indications for liver transplantation were adenomatosis in 1 and Budd Chiari in 1 patient.

Table S2. Sensitivity Analysis of Primary Outcome

End point	Machine Perfusion vs. Control	
	Risk Ratio	95% Confidence Interval
Symptomatic non-anastomotic biliary strictures (NAS)		
Intention to treat analysis (n=156)		
Unadjusted	0.36	0.14 – 0.94
Adjusted for prespecified covariates*	0.35	0.14 – 0.92
Adjusted post-hoc incl. static CIT*†	0.36	0.13 – 0.97
Per protocol analysis‡ (n=133)		
Unadjusted	0.36	0.14 – 0.95
Adjusted for prespecified covariates*	0.37	0.14 – 0.96

** Results are based on log-binomial regression modeling of the interaction between machine perfusion and NAS, with stratification factors (trial site and primary sclerosing cholangitis) and prespecified donor risk factors (donor risk index and donor warm ischemia time) as covariates.*

† CIT, cold ischemia time.

‡ Per protocol analysis included all patients with completed 6-months follow-up, including trial magnetic resonance cholangiography in patients not previously diagnosed with symptomatic NAS.

Table S3. Reasons for Missing Protocol Cholangiographies			
Reason*	**Machine Perfusion Group**	**Control Group**	**Total Number**
Graft loss prior to trial MRC at 6 months†			
Due to patient death	6	2	8
Due to retransplantation (non-biliary causes)	1	1	2
Patient-related reasons			
Metastasized hepatocellular carcinoma	1	-	1
Patient did not show up	-	1	1
Investigator-related reasons			
Forgotten to order by local investigator	3	1	4
Images available but of insufficient quality	1	6	7
Total	12	11	23

** None of these patients had clinical signs of cholangiopathy*

† MRC, magnetic resonance cholangiography

Table S4. Cross Tabulation of Symptomatic versus Radiological Non-anastomotic Biliary Strictures (NAS)				
		Symptomatic NAS		
		No	**Yes**	**Total**
Radiological NAS	**No**	40 (35%)	0	40 (30%)
	Yes	74 (65%)	19 (100%)	93 (70%)
Total		114	19	133

Table S5. Comparison of Cholestatic Laboratory Tests in Patients with Asymptomatic and Symptomatic Non-anastomotic Biliary Strictures				
		Symptomatic NAS		
Laboratory variable		**No (n = 74)**		**Yes (n=19)**
3 months post-transplant	*No.at Risk/Missing*	*Median (IQR)*	*No.at Risk/Missing*	*Median (IQR)*
Alkaline Phosphatase - U/L	72/3	**109** (77-231)	18/2	**302** (256-717)
Gamma Glutamyl Transferase - U/L	72/1	**60** (34-220)	18/-	**465** (169-905)
Bilirubin - µmol/L*	72/-	**7** (6-11)	18/-	**17** (9-34)
6 months post-transplant				
Alkaline Phosphatase - U/L	72/2	**110** (80-263)	17/-	**450** (218-725)
Gamma Glutamyl Transferase - U/L	72/2	**83** (30-193)	17/-	**289** (199-629)
Bilirubin - µmol/L*	72/-	**8** (5-15)	17/-	**22** (9-67)

NAS denotes non-anastomotic biliary strictures; IQR, interquartile range.

* To convert results for serum bilirubin from µmol/L to mg/dL, divide results by 17.1.

Table S6. Cross Tabulation of Radiological Severity of Biliary Abnormalities in Patients With or Without Clinically Symptomatic Non-anastomotic Biliary Strictures				
		Symptomatic NAS		
		No	**Yes**	**Total**
Radiological Severity Grading	**None**	40 (35%)	0	40 (30%)
	Mild	39 (34%)	6 (32%)	45 (34%)
	Moderate	25 (22%)	8 (42%)	33 (25%)
	Severe	10 (9%)	5 (26%)	15 (11%)
Total		114	19	133

NAS denotes non-anastomotic biliary strictures. P value = 0.003 (Chi-square test)

Table S7. Cross Tabulation of Radiological Severity of Asymptomatic Non-anastomotic Biliary Strictures in The Two Study Groups				
		Machine Perfusion	**Control**	**Total**
Radiologic Severity Grading	**Mild**	21 (49%)	18 (58%)	39 (53%)
	Moderate	15 (35%)	10 (32%)	25 (34%)
	Severe	7 (16%)	3 (10%)	10 (13%)
Total		43	31	74

P value = 0.64 (Chi-square test)

Table S8. Grading of Adverse Events in Each Study Group*			
Complication	**Machine Perfusion (n=78)**	**Control (n=78)**	**P value**
Grade 2	311 / 69	315 / 72	0.42
Grade 3a	59 / 41	78 / 39	0.75
Grade 3b	16 / 13	20 / 17	0.42
Grade 4a	25 / 16	32 / 16	1.00
Grade 4b	1 / 1	2 / 2	1.00

* Complications were graded according to the Clavien-Dindo classification[16] and are presented as number of complications and number of patients with a complication. P values refer to comparison of numbers of patients.

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