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Response to: Comment on: Pancreatectomy With Islet-Autotransplantation as Alternative for Pancreato-Duodenectomy in Patients With a High-Risk for Postoperative Pancreatic Fistula: The Jury Is Still Out

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We thank Dr Thomas Frederik Stoop and colleagues for their keen interest in our study[1] and their words of appreciation for our work.

The first issue raised by the authors relates to the risk–benefit balance of total pancreatectomy associated with islet-autotransplantation (TP-IAT) versus pancreatoduodenectomy (PD). As for whether postoperative morbidity is the ideal endpoint for our trial, we point out that the 90-day overall complication rate is the standard primary endpoint of many studies on this topic. Furthermore, as for our trial is concerned, it was an unavoidable choice to ensure study feasibility. In facts, considering the 90-day mortality rate as primary outcome, 464 patients would be needed to detect a statistical difference with adequate power, an unrealistic sample size for a prospective randomized trial on autologous islet transplantation in candidates for pancreatic surgery and at high risk for POPF. Consequently, overall, disease-specific and disease-free survival were included as secondary endpoints. However, the point raised by Stoop and colleagues actually implies a question that goes beyond the results of our trial, namely whether primary total pancreatectomy (TP) in patients at high risk of POPF is justified and preferable to pancreaticoduodenectomy. This question is still very open, and our results suggest that there may be room for an approach based on TP. In our study, as in other recent retrospective single-center series,[2-3] a 2%–4% mortality rate after TP is reported and, even in daily clinical practice, the 90-day mortality rate was 4% in centers performing more than 60 PDs per year.[4] We are aware of and appreciate the results of the Dutch PORSCH trial, but that study population was not selected for being at high risk of POPF, and therefore, the results of PORSCH cannot be extrapolated to the patients enrolled in our study. A major contribution to the discussion on this topic will be hopefully provided by the recently initiated TETRIS study (NCT05212350), a multicenter RCT in a cohort of patients with a very high risk of POPF, comparing TP and primary pancreatic anastomosis for postoperative outcomes and quality of life.

The second issue raised is related to the patient-reported outcomes. We fully agree that quality of life overtime is a highly relevant endpoint when determining the impact of TP on the life of our patients and their families. However, our study was not an appropriate setting to provide meaningful data on this issue. In fact, the heterogeneity of the underlying pancreatic diseases in terms of disease severity and the various adjuvant treatments patients had faced for extended periods of time after surgery were likely to have had a significant impact on patients' relevant outcomes.

The third issue relates to the relevance of glucose control. Islet-autotransplantation resulted in at least partial endogenous insulin secretion in around 90% of patients undergoing TP and good metabolic control at the last follow-up [day 388 (235–1307)] in 62% of the patients without severe hypoglycemic episodes or diabetes-related mortality. We were impressed by the recent results of the Dutch Pancreatic Cancer Group using a bihormonal artificial pancreas in 12 patients after TP. The 7-day follow-up in 9 of the 12 patients who completed the study showed an increased time spent between 70 and 180 mg/dL (time in range) of glucose levels. We hope these data will be confirmed through larger and longer RCTs involving unselected patients who underwent TP. We envision islet transplantation not as an alternative to the use of exogenous insulin and glucose sensor or delivery technology in patients with TP, but as a complementary and synergistic treatment for diabetes following TP since the bihormonal artificial pancreas hopefully wish to perform even better in patients with autologous islet transplantation after TP.

We completely agree with Stoop and colleagues that the jury is still out. However, our study confirmed that IAT is a feasible choice in patients with pancreas diseases other than chronic pancreatitis, and this should be viewed as an important advance in the field. The decision to perform TP-IAT requires assessing the risk–benefit ratio of this procedure in each individual case and should be discussed with the candidate patient in the context of multidisciplinary teams. High-volume referral centers for pancreatic surgery should be encouraged to collaborate with an islet isolation facility to provide access to IAT when appropriate. At last, in our conclusion, we used "may" to convey a degree of uncertainty. The results of our study are not a final ruling and we hope the jury is still out also for Stoop and colleagues in their appreciation for the potentials of TP-IAT.

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