CONSENSUS STATEMENT

# Summary of the International Society for Heart and Lung Transplantation (ISHLT) Consensus Conference on Graft Dysfunction within the First 72 hours after Heart Transplantation: A 10-year Update

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Primary graft dysfunction (PGD), defined as ventricular dysfunction occurring within 24 hours after heart transplantation (HTx) in the absence of identifiable secondary causes, remains a major contributor to early post-transplant mortality. Over the past decade, there has been a growing understanding of the burden of PGD, the clinical relevance of PGD classification and severity grading, and efforts to identify donor-, recipient-, and procedural-related risk factors and biomarkers predictive of PGD. Significant advancements have been made in donor heart preservation and procurement technologies, as well as in utilization and outcomes of mechanical circulatory support for managing severe PGD patients. However, existing risk-stratification tools have limitations and perform poorly in predicting PGD in the contemporary era. In addition, prevention and management strategies of PGD remain variable, largely influenced by center-specific practices and the lack of objective data. Moreover, vasoplegia often co-exists with PGD, and their complex interplay remains incompletely understood. To address these gaps, a consensus conference was organized on April 9, 2024, endorsed by the International Society for Heart and Lung

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*Abbreviations:* EGD, Early graft dysfunction; HTx, Heart transplantation; ISHLT, International Society for Heart and Lung Transplantation; IVIG, Intravenous immunoglobulin; LVAD, left ventricular assist device; MCS, Mechanical circulatory support; PGD, Primary graft dysfunction; RVAD, Right ventricular assist device; SGD, Secondary graft dysfunction; sEGD, Subsequent Early Graft Dysfunction; SVR, Systemic vascular resistance; TPE, Therapeutic plasma exchange; VA-ECMO, Veno-arterial extracorporeal membrane oxygenation

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Transplantation. The conference represented a collaborative multidisciplinary effort by international experts in cardiothoracic transplantation to reassess the consensus definition and grading of PGD, established more than a decade ago, and provide guidance on the utility of risk stratification tools, potential strategies to mitigate the risk of PGD, and the efficacy of current treatment options. The nature of this consensus is to establish a foundation and pave the way for future studies. Findings and consensus statements are presented.
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**KEYWORDS:**
Primary graft dysfunction; Early graft dysfunction; Treatment; Outcomes; Heart transplantation; Biomarkers; Vasoplegia

## 1. BACKGROUND

Although survival after heart transplantation (HTx) has improved significantly over the past 4 decades, primary graft dysfunction (PGD) remains a major contributor to early post-transplant mortality.[1] Until 2014, the HTx community lacked a standardized definition of PGD. This gap was addressed by the 2014 consensus conference on PGD, which provided a uniform definition and a grading severity scale.[2] Based on this definition and according to a recent meta-analysis of 8,120 patients included in 30 studies published between 2014 and 2020, the estimated overall pooled incidence of PGD (within 24 hours) was 20.5% (95% CI [17.2%-24.1%]), with severe PGD occurring in 7.7% of recipients and associated with the worst prognosis.[1]

Over the past decade, there has been a growing understanding of donor-, recipient-, and procedural-related risk factors and biomarkers predictive of PGD.[3–11] Significant advancements have been made in donor heart preservation and procurement technologies.[12–14] This, along with increased utilization of mechanical circulatory support (MCS) in PGD has resulted in improvement in outcomes for patients with severe PGD.[15–17] While the pathophysiology of PGD remains elusive, there is emerging evidence that links PGD to myocardial injury and the inflammatory milieu.[11] Additionally, there is a growing body of contemporary risk-stratification tools and ongoing research to further refine current definitions.[3]

Current prevention and management strategies for PGD remain variable, largely due to a lack of objective data, variations in reporting methods and standards, and center-specific practices, all of which further limit the interpretation and generalizability of published findings. Moreover, vasoplegia, a status of refractory vasodilatory shock, often co-exists with PGD, and their interplay is yet to be fully understood.[2,18,19]

The 2024 Consensus Conference on PGD, sponsored jointly by the International Society for Heart and Lung Transplantation (ISHLT) and the California Heart Foundation/Cedars-Sinai Smidt Heart Institute, was designed to provide a forum for an in-depth discussion among the leading experts in the field and to evaluate evolving science in this area as part of a 10-year update to the 2013-2014 ISHLT Consensus Conference on PGD.[2] This consensus conference took place on April 9, 2024, and included 19 U.S. and 37 international experts in HTx, including cardiologists, cardiac surgeons, anesthesiologists, and intensive care specialists. The objectives were:

- To educate the HTx community on the current understanding of PGD in HTx patients.
- To reassess the ISHLT PGD definition and grading scale based on current practices and outcomes.
- To describe risk factors for the development of PGD and its impact on outcomes in HTx.
- To assess the novel procurement and preservation approaches and their association with the risk of PGD.
- To assess the utility of treatments for PGD based on risk stratification.
- To review the working definitions of perioperative vasoplegia and discuss the interaction of PGD and vasoplegia syndromes.

After didactic sessions, the participants were divided into 3 breakout groups to discuss current issues in PGD after HTx, as well as unmet needs. Six primary questions arose from 4 pre-meeting conference calls for the breakout groups to consider (See Supplementary Materials II and IV).

The conference represented a collaborative multidisciplinary effort to reassess the consensus definition and grading of PGD, established more than a decade ago, and provide guidance on the utility of risk stratification tools, potential strategies to mitigate the risk of PGD, and the efficacy of current treatment options. We hope that this conference will pave the way for further detailed studies.

# 2. COMMUNITY SURVEY OF HEART TRANSPLANT PROGRAMS

Prior to the in-person consensus conference, a 22-question web-based survey of 64 transplant programs around the world was conducted. This survey aimed to assess the opinions of a broad group of stakeholders about their perspectives on definitions, outcomes, and risk factors, as well as prevention, perioperative practices, and management of PGD. The survey results are summarized in Table 1, and complete survey questions and results are included in Supplementary Materials V. Responses to select questions are listed below:

- Thirty-nine percent of the centers considered the first 24 hours after transplant as the ideal time to define PGD, while 25% selected 48 hours. Time frames within 6 (4.7%), 12 (12.5%), or 72 (7.8%) hours were less frequently chosen. Only a few participants thought it should be defined intraoperatively (2%) or at any time (3%) [Number of responses = 64].
- Total ischemic time (78%), donor age (52%), and > 20% donor under sizing by predicted heart mass (30%) were selected as the 3 most relevant donor risk factors for severe PGD by the participants. Other donor risk factors included vasopressor use, donor cause of death, abnormal left ventricular ejection fraction (LVEF) at procurement, and left ventricular hypertrophy, among others [Number of responses = 63].
- Pre-transplant veno-arterial extracorporeal membrane oxygenation (VA-ECMO) (54%), durable left ventricular assist device (LVAD) (46%), and decompensated hemodynamics pre-HTx (35%) were selected as the 3 most relevant recipient risk factors for severe PGD by the participants. Other recipient risk factors included inotrope use, amiodarone use, vasodilator use, and the need for acute dialysis pre-transplant, among others [Number of responses = 63].
- In terms of pre-transplant PGD prevention practices, 44% of centers would modify the use of amiodarone, angiotensin receptor-neprilysin inhibitor, and other guideline-directed medical therapies for patients at high risk for development of PGD. [Number of responses = 54].
- For the management of severe PGD, VA-ECMO (central, femoral-femoral, or subclavian-femoral) was cited as the most common MCS device used (62.5%), followed by intra-aortic balloon pump (IABP) (22%) and microaxial flow Impella (14.1%) [Number of responses = 64].
- Regarding the threshold to use VA-ECMO, 59% of centers reported that the threshold has been lower for use of VA-ECMO in recent years, while 20.3% stated that the threshold did not change [Number of responses = 64].
- Aside from inotropes/pressors and VA-ECMO, some centers would use induction therapy with anti-thymocyte globulin (42%), plasmapheresis (31%), and levosimendan (29%) to treat severe PGD [Number of responses = 52].

# 3. FINDINGS

## 3.1. Question 1. Should the PGD definition be completely reassessed? How?

### 3.1.1. Background

According to the 2014 PGD consensus conference report, graft dysfunction is categorized as either primary, defined as idiopathic ventricular dysfunction during the immediate 24-hour post-transplant period affecting either or both ventricles, or secondary graft dysfunction (SGD), arising from known causes such as hyperacute rejection, pulmonary hypertension (PH), or known surgical complications, among others.[2] This standardized PGD definition facilitated further studies investigating the incidence, risk factors, pathophysiology, and outcomes of PGD.[1,3]

Although the current definition of PGD has been broadly accepted, the diagnosis of graft dysfunction as "primary" or "secondary" often remains arbitrary. Misconceptions persist within the transplant community, with some providers continuing to attribute PGD to identifiable causes such as hemorrhage.[20]

Clinically, PGD patients may present with low cardiac output and hypotension despite adequate filling pressures in the setting of isolated right, left, or biventricular dysfunction.[21] Intraoperatively, if a patient fails to wean from cardiopulmonary bypass (CPB) or requires multiple high-dose inotropic agents to permit separation from CPB—this is classified as "immediate presentation," and MCS becomes necessary.[22,23] However, within the first 24 hours post-HTx, a "delayed presentation" of PGD may manifest following successful weaning from CPB and transfer from the operating room to the intensive care unit (ICU).[20,24,25] Less is known about the incidence of these forms of PGD phenotypes. In a study from Spain of 242 patients who developed severe PGD, 59.1% of the

**Table 1** Results of the Pre-Conference Online Survey

| | |
|---|---|
| PGD definition and outcomes | • Thirty-nine percent of the centers considered the first 24 hours after transplant as the ideal time to define PGD, while 25% selected 48 hours. Time frames within 6 (4.7%), 12 (12.5%), or 72 (7.8%) hours were less frequently chosen. Only a few participants thought it should be defined intra-operatively (2%), or at any time (3%) [Number of responses = 64].<br>• Forty-seven percent of the participants reported that ≥ 50% of patients experiencing severe PGD had concomitant vasoplegia (need for methylene blue or high-dose pressors with low SVR). [Number of responses = 59]<br>• Of the participants, 59% agreed with the use of the inotrope score to define moderate PGD as described in the 2014 PGD severity scale. [Number of responses = 63]<br>• When asked about 30-day mortality rate among patients experiencing severe PGD between 01/2013 and 01/2023, 40% of the participants cited a 30-day mortality of 30% or higher. [Number of responses = 62] |
| Risk factors for PGD | • Total ischemic time (78%), donor age (52%), and donor under sizing >20% by predicted heart mass (30%) were selected as the 3 most relevant donor risk factors for severe PGD by the participants. Other donor risk factors included vasopressor use, donor cause of death, abnormal LVEF at procurement, and left ventricular hypertrophy, among others [Number of responses = 63].<br>• Pre-transplant veno-arterial extracorporeal membrane oxygenation (VA-ECMO) (54%), durable left ventricular assist device (LVAD) (46%), and decompensated hemodynamics pre-HTx (35%) were selected as the 3 most relevant recipient risk factors for severe PGD by the participants. Other recipient risk factors included inotrope use, amiodarone use, vasodilator use, and the need for acute dialysis pre-transplant, among others [Number of responses = 63]. |
| PGD prevention and peri-operative practices | • In terms of pre-transplant PGD prevention practices, 44% of centers would modify the use of amiodarone, angiotensin receptor-neprilysin inhibitor, and other guideline-directed medical therapies for patients at high risk for development of PGD. [Number of responses = 54].<br>• When asked on donor heart storage or perfusion methods utilized, SherpaPak, Organ Care System, and Ex-Vivo were used in 51%, 43%, and 18% of the centers, respectively [Number of responses = 51].<br>• Participating centers cited SherpaPak (33%) and Organ Care System (24%) as the most used donor heart storage or perfusion systems [Number of responses = 49], with 54% of the centers procuring at least 21% of donor hearts using donor heart storage or perfusion systems [Number of responses = 54].<br>• In centers where ex-vivo perfusion is utilized, 35.1% of the participants felt that this method has decreased the incidence of PGD. [Number of responses = 37].<br>• Most used cardioplegic solutions at participating transplant centers were Bretschneider (Custodiol) (31.67%), UW (25%), and Celsior (16.67%) [Number of responses = 60].<br>• For patients on VA-ECMO going into transplant, 52% of the centers would routinely wean VA-ECMO immediately after transplant [Number of responses = 64].<br>• In terms of post-operative routine practices, 87.5% of the centers would assess hemodynamics with swan immediately post-operatively [Number of responses = 64], and 95% would perform transesophageal echocardiogram intraoperatively or immediately post-HTx to assess the graft function [Number of responses = 63]. |
| PGD management | • For the management of severe PGD, VA-ECMO (central, femoral-femoral, or subclavian-femoral) was cited as the most common mechanical circulatory support (MCS) device used (62.5%), followed by intra-aortic balloon pump (22%) and microaxial flow Impella (14.1%). [Number of responses = 64].<br>• Regarding the threshold to use VA-ECMO, 59% of centers reported that the threshold has been lower for the use of VA-ECMO in recent years, while 20.3% stated that the threshold did not change. [Number of responses = 64].<br>• Aside from inotropes/pressors and VA-ECMO, some centers would use induction therapy with anti-thymocyte globulin (42%), plasmapheresis (31%), and levosimendan (29%) to treat severe PGD [Number of responses = 52].<br>• For high-risk PGD cases, 23% and 30% of the centers would use Cytosorb or plasmapheresis, respectively.<br>• For the management of PGD, 55% of the centers uses induction therapy [Number of responses = 62], with anti-thymocyte globulin being the most utilized induction therapy (70%) [Number of responses= 34].<br>• Heart re-transplantation was cited as an option to treat patients suffering from PGD in 57% of the centers [Number of responses = 63]. |

Abbreviations: LVEF, Left ventricular ejection fraction; PGD, Primary graft dysfunction; SVR, Systemic vascular resistance; VA-ECMO, Veno-arterial extracorporeal membrane oxygenation.

patients required intraoperative implantation of MCS.[24] Similarly, a UK-based study by Lim et al, including 216 patients (67 experienced severe graft dysfunction within 24 hours), found that 64.2% of patients presented immediately. The authors also reported a markedly higher 1-year mortality rate for the immediate presentation

group as compared to the delayed presentation group (35% vs 8%, $p < 0.0001$).[20] In another study from the US, including 47 patients with severe PGD, about 34% of the cases had an immediate presentation. Compared with patients with delayed presentation, those with immediate presentation had significantly increased mortality rates at 30 days and 1-year post-HTx.[25] These findings underscore the prognostic utility of the PGD presentation timing within the 24-hour period—whether immediate or delayed, and their distinct hemodynamic implications.[20,26]

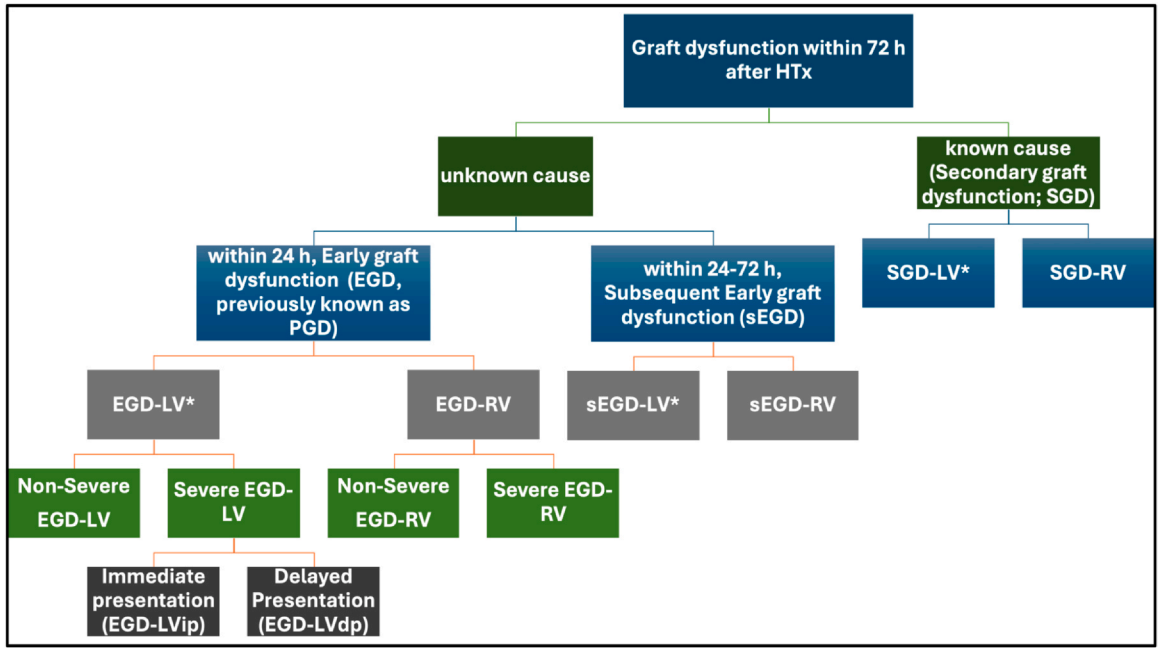
### 3.1.2. Breakout group discussions

Participants agreed that the timing of PGD should remain within 24 hours after transplant but that cases with graft dysfunction within the first 72 hours after transplant should be categorized into those with a discernible cause and those without a known cause (Figure 1). To accommodate a broader scope of graft dysfunction immediately after transplant, a new nomenclature would be used in place of PGD. Cases with unknown cause should be classified into Early (EGD, within 24 hours post-HTx, previously known as PGD) or subsequent early graft dysfunction (sEGD, within 24-72 hours post-HTx). The participants supported replacing PGD terminology with "early graft dysfunction (EGD)." Similar to the old PGD scale, discussants also emphasized the need to distinguish left ventricular/biventricular from isolated right ventricular EGD or sEGD, given the differences in underlying etiologies. Notably, there was a consensus on the need to delineate the time frame of presentation with EGD-LV into failure to wean from CPB ("immediate") vs occurring after successful weaning from CPB ("delayed").

### 3.1.3. Consensus statements

**#1.** Graft dysfunction within the first 72 hours after transplant is to be further categorized into cases with a discernible cause (secondary graft dysfunction, SGD) and those with an unknown cause (Figure 1).
**#2.** Graft dysfunction with unknown cause should be further classified into early graft dysfunction occurring < 24 h hours post-HTx (EGD), which replaces the previous term of PGD; or subsequent early graft dysfunction at 24-72 hours post-HTx (sEGD).

**Figure 1** Revised classification of graft dysfunction after heart transplantation based on the underlying cause and timing of presentation. Abbreviations: CPB, cardiopulmonary bypass; EGD, early graft dysfunction; EGD-LVip, early graft dysfunction with the immediate presentation; EGD-LVdp, early graft dysfunction with the delayed presentation; LV, left ventricle; RV, right ventricle; PGD, primary graft dysfunction, sEGD, Subsequent Early Graft Dysfunction, SGD: Secondary Graft Dysfunction. *Including left ventricular or biventricular dysfunction.



**#3** EGD and sEGD to be further classified into LV (Left ventricular or biventricular dysfunction) or RV (Isolated right ventricular dysfunction).
**#4.** Severe EGD-LV should be further categorized based on the timing of presentation into Immediate Presentation (EGD-LVip, failure to wean from cardiopulmonary bypass) or Delayed Presentation (EGD-LVdp, occurring after successful weaning from cardiopulmonary bypass), as this timing appears to hold significant prognostic value (Figure 1).

## 3.2. Question 2. Should the current PGD scale for severity be revised?

### 3.2.1. Background

The 2014 PGD consensus conference divided PGD into 2 major groups: PGD-LV for isolated left ventricular or biventricular failure and PGD-RV for isolated right ventricular involvement.[2] For PGD-LV, a 3-grade severity system was provided, including mild, moderate, and severe PGD descriptors (Table 2).[2] Subsequently, several epidemiological studies have provided insights into the burden and prognostic value of these grades.[1] In a recent meta-analysis, the pooled incidence of mild, moderate, and severe PGD-LV was 3.5%, 6.6%, and 7.7%, while 1-year mortality rates were estimated at 15%, 21%, and 41%, respectively.[1] Sabatino et al highlighted in their analysis of HTx patients at 2 Italian centers between 1999 and 2013 the clinical relevance of the PGD severity grading, with moderate and severe grades being associated with progressively worse outcomes, while mild grades did not seem prognostically meaningful.[27] In fact, the mild/moderate grading is based on the calculated inotrope score, and rapid escalation from mild to moderate due to physician-directed vasoactive/inotropic therapies warrants careful consideration. During the Australian and New Zealand trial of Hypothermic Oxygenated Perfusion (HOPE) preservation of donor hearts,[28,29] the inotrope score was inflated by the disproportionate impact of norepinephrine, resulting in upcoding mild PGD cases to moderate grade. Kaye et al recently conducted a retrospective study of 50 HTx recipients, calculated the inotrope scores, and found that 82% of the patients had an inotrope score > 10. Of these patients, 27% had PGD, 20% had vasoplegia, and 46% had no clear evidence of PGD or vasoplegia based on case review, raising concerns that the inclusion of norepinephrine in the inotrope score may overestimate the incidence of PGD, particularly when administered to patients with vasoplegic syndrome.[29] These findings suggest that the applicability of the inotrope score in PGD severity grading may be limited in current clinical practice.[29,30]

Severe PGD-LV is defined as LVEF ≤ 40% and dependence on left or biventricular mechanical support.[2] Findings from the International Consortium on PGD revealed a significantly increased incidence of severe PGD-LV over the past decade, which could be attributed to improved experience with and access to VA-ECMO, resulting in increased utilization in the operating room or within 24 hours of transplant, compared to a decade ago.[3] Other potential reasons for this observation include increased frequency of prolonged ischemia time and longer travel distances.[31] It is noteworthy that some centers follow a more aggressive approach with a higher tendency to initiate MCS or to maintain pre-HTx VA-ECMO after transplantation in patients who may no longer need it, which could potentially result in overestimating severe PGD incidence.[4,24] However, graft dysfunction (LVEF ≤ 40% and hemodynamic compromise) is still necessary for the new terminology of EGD-LV.

For PGD-RV, the 2014 consensus standardized PGD-RV definition did not include a severity scale (Table 2). PGD-RV has an incidence of 1.6% and 1-year mortality of 35%.[1] Alam et al suggested modifying PGD-RV criteria and introducing a grading scale, including a mild grade requiring no inotropes or low-dose inotropes for less than 72 hours post-HTx, a moderate grade for escalated inotropic therapy or the inability to wean off inotropes for more than 72 hours post-HTx, and a severe grade for the need for a right ventricular assist device.[32] Kaveevorayan et al used modified criteria to define isolated acute right ventricular failure (RVF) post-HTx; their criteria encompassed pulmonary capillary wedge pressure cut-off < 18 mmHg, elimination of the criteria for cardiac index (CI) < 2 L/min/m$^2$ with the use of multiple inotropes, and expanding time to diagnosis to the first 72 hours post-HTx. The authors reported a high RVF prevalence of 59%, which peaked (highest right atrial pressure) on day 3 following HTx. In contrast, only half of those patients with RVF met the ISHLT criteria for PGD-RV. The authors added that those who were defined as having RVF demonstrated worse BUN/creatinine trends than those who met the PGD-RV criteria. The authors argued that current ISHLT criteria may underestimate PGD-RV incidence and that a revision is needed to identify patients who might be at increased risk for adverse events.[33]

**Table 2** Revised Severity Classification for Early Graft Dysfunction (EGD) with Unknown Cause (Previously Known as Primary Graft Dysfunction)

| Classification | 2014 Classification: primary graft dysfunction (PGD) | Revised 2024 Classification: early graft dysfunction with unknown cause (EGD) |
|---|---|---|
| Left ventricular or biventricular dysfunction within 24 hours after transplant | *Mild:* one of the following:<br>● LVEF ≤ 40% by echocardiography,<br>● Hemodynamics with RAP > 15 mm Hg, PCWP > 20 mm Hg, CI < 2.0 L/min/m$^2$ (lasting more than 1 h) requiring low-dose inotropes | *Non-Severe EGD-LV:* Both of the following:<br>● LVEF ≤ 40%<br>● Hemodynamic compromise with RAP > 15 mm Hg, PCWP > 20 mm Hg, CI < 2.0 L/min/m$^2$, requiring inotropic support. |
| | *Moderate:* one from I and another criterion from II:<br>I. LVEF ≤ 40%, Hemodynamic compromise with RAP > 15 mm Hg, PCWP > 20 mm Hg, CI < 2.0 L/min/m$^2$, or hypotension with MAP < 70 mm Hg (lasting more than 1 h)<br>II. High-dose inotropes-Inotrope score > 10[a] or Newly placed IABP (regardless of inotropes) | |
| | *Severe:* Dependence on left or biventricular mechanical support, including ECMO, LVAD, BiVAD, or percutaneous LVAD. Excludes requirement for IABP. | *Severe EGD-LV:* All of the following:<br>● LVEF ≤ 40%<br>● Hemodynamic compromise with RAP > 15 mm Hg, PCWP > 20 mm Hg, CI < 2.0 L/min/m$^2$, requiring inotropic support.<br>● Necessitating left or biventricular mechanical support, including VA-ECMO*, surgical or percutaneous LVAD, BiVAD, or newly placed IABP<br>Additionally, Severe EGD-LV to be classified:<br>● EGD-LVip: Immediate presentation as failure to wean graft from cardiopulmonary bypass<br>or<br>● EGD-LVdp: Delayed presentation as graft failure occurring after successful weaning from cardiopulmonary bypass |
| Isolated right ventricular dysfunction within 24 hours after transplant | Diagnosis requires either both i and ii, or I, iii alone:<br>I. Hemodynamics with RAP > 15 mm Hg, PCWP < 15 mm Hg, CI < 2.0 L/min/m<br>II. TPG < 15 mm Hg and/or pulmonary artery systolic pressure < 50 mm Hg<br>III. Need for RVAD | *Non-Severe EGD-RV:* Both of the following:<br>● RVEF ≤ 35% and /or TAPSE < 1.6 cm<br>● Hemodynamics with RAP > 15 mm Hg, PCWP < 15 mm Hg, CI < 2.0 L/min/m2, requiring inotropic support; TPG < 15 mm Hg and/or pulmonary artery systolic pressure < 50 mm Hg |
| | | *Severe EGD-RV:* All of the following:<br>● RVEF ≤ 35% and /or TAPSE < 1.6 cm<br>● Hemodynamics with RAP > 15 mm Hg, PCWP < 15 mm Hg, CI < 2.0 L/min/m2, requiring inotropic support; TPG < 15 mm Hg and/or pulmonary artery systolic pressure < 50 mm Hg<br>● Necessitating MCS including VA-ECMO, surgical or percutaneous RVAD. |

Abbreviations: BiVAD, biventricular assist device; CI, cardiac index; IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; RVAD, right ventricular assist device; RVEF, right ventricular ejection fraction; TAPSE, Tricuspid Annular Plane Systolic Excursion; TPG, transpulmonary pressure gradient; VA-ECMO, Veno-arterial extracorporeal membrane oxygenation.

*Excluding patients placed on VA-ECMO pre-transplant and were maintained on VA-ECMO post-transplant due to institutional policies, despite the absence of a clinical indication.

### 3.2.2. Breakout group discussion

Most participants considered the use of the inotrope score for PGD grading as no longer practical. While the participants acknowledged the prognostic value of the current grading system, they suggested consolidating the severity scale of EGD-LV (including left or biventricular dysfunction) into 2 grades: non-severe and severe, the latter requiring initiation of MCS. It was noted that the prognosis of mild and moderate PGD was similar (not significantly different), so combining the 2 groups made sense. They also recommended applying this revised

grading scheme to EGD-RV (isolated right ventricular dysfunction). Detailed criteria for the revised grading scales are presented in Table 2. It is also important to have a direct correlation between the prior PGD grading scale and the revised EGD grading scale to be able to compare past to present data. It was acknowledged that the precise threshold for initiating MCS early after HTx varies among centers, which continues to be a limitation since MCS initiation is the core of the definition. Furthermore, some centers continue the use of VA-ECMO if patients were on VA-ECMO before transplantation. The participants debated that the condition should not be classified as EGD if MCS could be weaned within 24 hours. In addition, it was felt that placement of a new intra-aortic balloon pump (IABP) would qualify for severe EGD. In the past, previously placed IABPs confounded prognostic data. Importantly, graft dysfunction is still necessary for the diagnosis of EGD.

#### 3.2.3. Consensus statement

**#5.** EGD-LV and EGD-RV are to be classified into two grades: non-severe or severe, based on the need to initiate MCS for cardiac dysfunction after transplantation. The inotrope score will no longer be used for grading the severity of EGD (Table 2).

## 3.3. Question 3. What prediction models and/or biomarkers are reasonable to determine risk for PGD? Are there reported prevention strategies?

#### 3.3.1. Background

In the 2014 PGD consensus document, various donor, recipient, and procedural risk factors for PGD were identified.[2] Over the past decade, there has been a growing understanding of additional risk factors for PGD,[4–7,34,35] which include, but are not limited to, donor hyperoxia, donation after circulatory death (DCD), warm ischemic time in DCD, recipient male sex, durable LVAD as bridge to transplant, and recipient pre-transplant medications such as renin–angiotensin–aldosterone system (RAAS) inhibitors and amiodarone.[6,34–39] An updated list of EGD risk factors is presented in Table 3.

To risk stratify patients for the development of PGD, several clinical scoring models have been developed, most of which were designed and validated specifically in the context of donation after brain death (DBD).[7,43,41,44] Segovia et al developed the RADIAL score based on a single-center experience of 621 HTx recipients and identified 6 independent risk factors predictive of PGD (Right atrial pressure ≥10 mm Hg, recipient Age ≥60 years, Diabetes mellitus, Inotrope dependence, donor Age ≥30 years, Length of ischemic time ≥240 minutes—i.e., RADIAL), the incidence of PGD correlated strongly with higher scores.[43] The score was externally validated in a cohort of 698 HTx recipients from 14 Spanish centers.[45] It was also validated in a modified format, excluding the right atrial pressure, and was found to predict graft failure as well as long-term survival among a large patient cohort of 32,382 adults in the United Network for Organ Sharing (UNOS) database.[46] The PREDICTA score, based on data of 613 patients from 6 centers in the UK transplanted between 2012 and 2016, included recipient Preoperative MCS, DIabetes mellitus, CPB time > 180 minutes, implant Time, and donor Age. The PREDICTA score outperformed the RADIAL score (C-statistic of 0.704 vs. 0.547).[41] However, due to a lack of data on PREDICTA score components in larger studies or national transplant registries, the score was not externally validated. At Cedars-Sinai Medical Center, Benck et al developed the **ABCE** score using a machine learning approach for identifying risk factors for severe PGD in a single center.[7] The **ABCE** score included treatment with **A**CEI/**A**RB/**A**RNI plus MR**A**, treatment with amiodarone plus **B**eta-**B**locker, and prior **C**ardiac surgery, longer ischemic tim**E,** and was found to have acceptable discrimination for severe PGD with an AUC-ROC of 0.77.

Challenges in the broader applicability of these risk scores stem from variability in historical eras, patient populations, and center practices. Their predictive value is further limited by the specific variables used in models and the context in which they were evaluated. Additionally, the lack of granular perioperative data, particularly regarding donor characteristics, further hinders external validation and use of these scores.

The International Consortium on PGD was formed to identify the clinical risk factors for PGD in the contemporary era and to address the lack of registry-based datasets available. Data from 10 centers ($n = 2746$, 2010-2020) were analyzed.[3] The authors identified acute preoperative dialysis, durable LVAD support, and total ischemic time as significant predictors of severe PGD. Notably, the widely used RADIAL score performed poorly in this contemporary cohort. Subsequently, the consortium investigators developed PGD-AI, a machine learning model integrating 18 recipient, donor, and perioperative characteristics relevant to the current HTx era.[44] The

**Table 3** Donor, Recipient, and Procedural Risk Factors for EGD After Heart Transplantation (modified from Kobashigawa et al, 2014[2*]).

| Donor Factors | Recipient Factors | Procedural Factors |
|---|---|---|
| Age | Age | Donor-recipient sex mismatch (specifically female to male) |
| Comorbidities (coronary artery disease, diabetes, hypertension) | Male Sex[37] | Undersized donor hearts[40] |
| Valvular disease | Weight, BMI | Weight mismatch |
| Drug abuse | Comorbidities (renal dysfunction, liver dysfunction, diabetes) | Non-cardiac organ donation |
| Cause of death (e.g., intracranial hemorrhage) | Pre-transplant VA-ECMO | Experience of the procurement team and center volume |
| Sepsis | Durable LVAD[3,39] | Increased blood product transfusion requirement |
| Trauma | Complicated vs uncomplicated LVAD | Emergency vs Elective Transplant |
| Cardiac dysfunction/wall motion abnormalities/left ventricular hypertrophy | Pre-transplant mechanical ventilation | Cardioplegic solution |
| High inotropic requirements | Pre-transplant dialysis[3] | Increased total ischemic time |
| Hyperoxia[6] | Fixed or irreversible pulmonary hypertension | Prolonged CPB time[41] |
| Donation after circulatory death[38] | Right ventricular dysfunction as assessed by CVP/PCWP ratio[39] | Prolonged implant time[41] |
| Prolonged aWIT in donors after circulatory death[34] | Infection | Ischemia Reperfusion Injury |
| | Sensitization | |
| | Pre-transplant medications: RAAS inhibitors, beta-blockers, amiodarone,[6,7,35,36,39,42] | |
| | Complex surgery: congenital heart disease, multiple sternotomies, prior cardiac surgery, re-transplantation | |
| | Multiorgan transplant | |

Abbreviations: aWIT, asystolic warm ischemic time; CPB, cardiopulmonary bypass; CVP, central venous pressure; LVAD, left ventricular assist device; PVR, pulmonary vascular resistance; RAAS. Renin-Angiotensin-Aldosterone-System; VA-ECMO, veno-arterial extra-corporeal membrane oxygenation.

*The risk factors that are newly added compared to the 2014 consensus document are noted by the new references.

PGD-AI calculator was validated in an expanded cohort, including data from over 4,000 patients from 14 centres.[47] Furthermore, Moayedi et al validated the score in a contemporary cohort (2019-2023) at Toronto General Hospital, and the PGD-AI score outperformed the RADIAL score in predicting severe PGD.[48]

These models were primarily derived from DBD cohorts and may not adequately capture the unique physiological and procedural characteristics associated with DCD or the use of novel organ preservation technologies**.** In an analysis of the UNOS database, including 2590 HTx recipients between 09/2023 and 06/2024, DCD HTx recipients were more likely to experience severe PGD-LV (9.5% vs 5.1%, $p < 0.001$), as compared to DBD. However, PGD recovery rates at 72 hours, 30-day mortality, and length of hospital stay following transplantation were comparable between groups. In addition, no differences were noted in rates of PGD-LV between the direct procurement and preservation versus normothermic regional perfusion procurement methods.[38] Similarly, Ayer et al found that DCD heart transplant recipients were more likely to develop severe, biventricular PGD compared to DBD recipients but had shorter time on MCS and shorter hospital stay.[49] These findings suggest that patterns of graft dysfunction and recovery may differ between donor types, which could potentially be due to differences in underlying pathophysiology and procedural technique.

Several donor,[6,50–60] recipient,[8–10,61,62–65] and procedural [11,66–68] biomarkers have been suggested as potential predictors of PGD. While the underlying pathophysiology of PGD remains elusive, many of these biomarkers hint at biological evidence of myocardial injury and the inflammatory milieu involved in PGD. Elevated cardiac troponin I (cTnI) concentrations in the preservation solution from 43 HTx procedures have been

associated with the development of PGD.[66] Moreover, Jernryd et al found that creatine kinase-MB measured in the coronary effluent in donor hearts preserved by cold static storage may help identify recipients at increased risk for developing severe PGD.[11] Increased donor procalcitonin levels at the time of heart explant were suggested to predict early graft failure-related mortality.[55] Proteomic analyses of pretransplant recipient serum identified several proteins related to inflammation, coagulation, and activation of the innate immune system, including plasma kallikrein, peroxiredoxin, tropomyosin alpha-4, and myeloperoxidase, to be predictive of PGD development.[8] Similarly, increased plasma pro-inflammatory cytokine levels during the first 24 hours after reperfusion have been observed in patients who developed severe PGD.[9] Fine et al, in their pre-transplant serum exosome analyses, identified signaling pathways that may help differentiate patients who would later develop PGD-RV from PGD-LV.[69] Lastly, Truby et al identified CLEC-4c surface marker of plasmacytoid dendritic cells in recipient pre-transplant serum as a predictor of severe PGD in a large cohort with derivation and validation sets.[10] Table 4 summarizes potential biomarkers of EGD. While many of the biomarkers are investigational, they contribute to the growing understanding of PGD and shall help risk stratify, prevent, and identify therapeutic targets for PGD.

Current PGD prevention strategies focus on avoiding high-risk donor-recipient combinations, optimizing modifiable risk factors, and improving donor-recipient matching. Such strategies may include avoiding donor hyperoxia and avoiding donor-recipient undersizing ≥ 30% by predicted heart mass calculation, particularly in patients at high risk for PGD.[6,40]

In terms of donor heart preservation and transportation, D'Alessandro et al. reported in an analysis of 1,061 U.S. adult heart transplant recipients included in the Global Utilization and Registry Database for Improved Heart Preservation-Heart Registry that the use of controlled hypothermic preservation at 4-8 °C using the SherpaPak Cardiac Transport System (Paragonix Technologies, Inc., Waltham, MA) was associated with a 50% relative reduction in the incidence of severe PGD compared to transplants using ice storage (6.0% vs 12.1%, respectively; $p = 0.018$).[14] Moayedifar et al evaluated the use of the SherpaPak Cardiac Transport System for extended criteria donor heart preservation and transportation and found a significant reduction in the rate of all post-transplant MCS, new post-transplant ECMO/VAD, PGD, and severe PGD when compared to static ice storage.[70]

The HOPE randomized controlled trial evaluated the use of the XVIVO Heart Preservation System for donor hearts with a projected preservation time of 6 to 8 hours, and showed a reduced incidence of PGD with HOPE compared to standard ice storage.[13] The Organ Care System (OCS) EXPAND Trial evaluated the use of an extracorporeal normothermic perfusion system on donor heart utilization and post-transplant outcomes in

**Table 4** Clinical and Investigational Biomarkers of EGD After Heart Transplantation

| Donor | Recipient | Procedural |
|---|---|---|
| Troponin[51,52] | Albumin[61] | Point of care Troponin in preservation solution[66] |
| BNP[53] | Total Bilirubin[62] | Point of care CK-MB from the coronary sinus at HTx[11] |
| Hypernatremia[50] | Neutrophil-to-lymphocyte ratio[63] | Metabolomic profiling of ex-situ normothermic perfusion solution*[67] |
| Creatinine[6] | Pro-inflammatory Cytokines[9] | |
| TNF-α[54] | Proteomic profiling CLEC4C Expression[10] | |
| Procalcitonin[52,54,55] | pretransplant-recipient serum proteomics**[8] | |
| IL-6[56,57] | SERCA2a[62] | |
| SMARCAL-1[58] | GDF-15[64] | |
| HIF-1[59] | Neutrophil-to-lymphocyte ratio[63] | |
| VEGF-A[60] | | |

Abbreviations: BNP, B-type natriuretic peptide; CKMB, creatine kinase-MB; DPP, direct procurement and perfusion; DCD, donation after circulatory death; GDF-15, growth differentiation factor-15; HIF, hypoxia-inducible factor-1; HTx, heart transplant; SERCA2a, sarcoplasmic reticulum Ca2+ATPase 2a; SMARCAL-1, SWItch/sucrose non-fermentable, a matrix-associated, actin-dependent regulator of chromatin subfamily a-like 1; TNF-α, tumor necrosis factor-alpha; VEGF-A, vascular endothelial growth factor

*Pattern of fuel substrate utilization that correlates with subclinical and clinical allograft dysfunction.

**Plasma kallikrein, peroxiredoxin, tropomyosin alpha-4, and myeloperoxidase.

extended criteria donor hearts after brain death (DBD). The study revealed that the use of the Organ Care System for extended criteria donor hearts resulted in low rates of severe PGD (6.7%) and comparable 86% patient survival at 2 years post-transplant.[12]

A reduction in PGD incidence has also been observed with the use of a leukocyte-depleting filter combined with regular antegrade administration of Buckberg cold blood cardioplegia.[71] Continuous cold blood cardioplegia, followed by controlled reperfusion of warm blood, resulted in similar findings.[72] These findings were further supported by data from a contemporary cohort in the UK using continuous antegrade perfusion.[73]

For recipient-related prevention measures, there has been limited evidence supporting discontinuation of RAAS inhibitors and amiodarone pretransplant, given their contribution to increased risk of PGD,[7,35,42,74] but more data is needed to guide these recommendations.

#### 3.3.2. Breakout group discussion

Participants agreed that EGD is driven by multiple risk factors; therefore, a careful evaluation of donor, preservation and implantation, and recipient characteristics is essential for timely diagnosis and management (Table 4). Discussants acknowledged that while current PGD risk scores have clinical predictive value, further work is necessary to address their limitations. This could be achieved through international registries and incorporating AI and machine learning modeling approaches. Discussants emphasized the need for biomarkers that can risk-stratify patients for the development of EGD, inform underlying pathophysiology, grade EGD severity, differentiate between EGD-RV and EGD-LV, and provide insights into recovery of allograft function. However, they noted that available biomarkers are not widely used globally and are subject to unclear pathophysiology. In addition, investigational biomarkers are not accessible in a timeframe that is useful. Some participants opined that donor biomarkers, such as troponin, have not been informative. The potential utility for serial monitoring of perfusates or coronary sinus sampling was also discussed. EGD prevention strategies were discussed, including optimization of modifiable risk factors and utilization of novel organ preservation technologies. Several participants supported discontinuation of amiodarone pre-transplant if possible and believed that holding RAAS inhibitors and vasodilators 24 hours prior to transplant would be beneficial. However, further studies are needed to strengthen the evidence supporting these practices.

#### 3.3.3. Consensus statements

**#6.** Evaluation of donor, procedural, and recipient EGD risk factors is essential to guide EGD prevention and management strategies. Avoiding high-risk combinations and addressing modifiable risk factors, when possible, are likely to improve outcomes.
**#7.** Building registries with comprehensive data on pre-transplant recipient and donor characteristics, preservation and management strategies, and associated clinical outcomes of patients with EGD and incorporating artificial intelligence and machine learning approaches may help identify risk factors, refine definitions, and serve as the foundation for rigorous clinical trials.
**#8.** The use of novel organ preservation and transportation technologies may mitigate the risk of EGD development.
**#9.** Discontinuation of amiodarone in patients listed for HTx and holding RAAS inhibitors prior to surgery may reduce the risk of EGD.

### 3.4. Question 4. Are there specific treatment strategies for PGD that should be included in this update?

#### 3.4.1. Background

The first step in the management of suspected EGD is to exclude any known underlying causes of graft dysfunction.[75] In general, the treatment of EGD is supportive and begins with escalating inotropic support, with careful assessment of graft function, monitoring of hemodynamics, and continuing to evaluate for any reversible contributors.[21,22,75] The choice of specific pharmacological agents is usually based on institutional protocols/provider choice informed by clinical evaluation and patient responsiveness. Levosimendan is a calcium-sensitizing agent that modulates positive inotropic and vasodilatory effects.[76–78] Weis et al reported a case series of 12 patients with PGD who received levosimendan for PGD; 11 of the 12 patients survived beyond 30 days, with significant reductions in inotropic support and without necessitating MCS.[76] However, the same group had significantly lower 1- and 3-year survival rates compared with

patients without EGD.[77] A recent study by Immohr et al showed that early drug therapy with levosimendan (within 48 hours) in patients with severe PGD supported with VA-ECMO ($n = 23$) reduced the duration of MCS, reduced perioperative morbidity, and requirement for blood transfusions.[78]

If the patient has RV dysfunction (with or without PH), inhaled pulmonary vasodilators with minimal effect on systemic arterial pressure, such as nitric oxide or prostacyclin analogues, should be considered.[23]

In those who fail to maintain adequate hemodynamics despite pharmacologic therapy due to isolated right, left, or biventricular dysfunction, support should escalate to IABP or other MCS.[22,75] However, the decision of the type of MCS device, timing of initiation, and cannulation strategies varies according to each center's preferences and experience with effective approaches. Guo et al, in their single-center experience of 39 severe PGD patients requiring VA-ECMO, demonstrated how adopting institutional protocols involving additional objective criteria for VA-ECMO and partial-flow support implementation, and use of chimney graft arterial cannulation, resulted in significantly improved survival.[17]

Takeda et al compared the use of VA-ECMO vs continuous-flow extracorporeal LVAD in patients with severe PGD-LV and found that the VA-ECMO group had a lower incidence of major bleeding requiring chest re-exploration (30% vs 77%, $p = 0.0047$), lower incidence of renal failure requiring renal replacement therapy (11% vs 53%, $p = 0.0045$), a trend towards increased in-hospital survival (81% vs 59%, $p = 0.16$), and a higher rate of graft recovery (89 vs 59%, $p = 0.03$). The 3-year post-transplant survival was 66% and 41% ($p = 0.013$) in the VA-ECMO and LVAD groups, respectively. [79] Notably, several studies have reported favorable survival in patients who were weaned off VA-ECMO for severe PGD, with comparable survival at 1 year to patients who did not experience PGD.[80,81] However, these findings should be interpreted with caution due to the relatively high mortality rate among patients who did not develop PGD in these studies.

Early initiation of VA-ECMO in patients with severe PGD has been associated with improved myocardial recovery, leading to better clinical outcomes.[82–84] DeRoo et al compared institutional adoption of prompt VA-ECMO cannulation vs a historical group of conservative VA-ECMO initiation. The median time to cannulation was 1.95 and 7.26 hours in the prompt and conservative groups, respectively. The prompt group had a trend towards improved in-hospital (95% vs 72%, $p = 0.08$) and 1-year (90% vs 67%; $p = 0.1$) survival, with no significant differences in ICU length of stay or the incidence of major adverse events.[83] However, a larger study from Spain involving 242 patients with severe PGD found no differences in 3-month and 1-year survival between patients who underwent early MCS initiation (< 3 hours post-transplant, representing 70.7% of the cohort) and those who were managed with a more conservative approach with deferred MCS initiation (> 3 hours post-transplant).[24]

Notably, some centers have observed that institutional protocols emphasizing prolonged reperfusion prior to MCS implantation may influence post-transplant MCS utilization. In certain protocols, implementing a standardized period of graft support with CPB (e.g., ≥60 minutes) before escalating to MCS has been associated with a reduced need for post-transplant MCS. This suggests that allowing sufficient time for myocardial recovery before committing to short-term assist devices may be beneficial in select cases, recognizing that while some hearts will ultimately require MCS, others may regain function with extended CPB support alone. However, further studies are needed to validate these observations and define optimal reperfusion strategies.

Current evidence suggests potential survival benefit of peripheral over central VA-ECMO cannulation in patients with severe PGD. A recent meta-analysis, including 16 studies with 874 patients, showed that peripheral cannulation was associated with a nonsignificant reduction in short-term mortality, including in-hospital mortality or 30-day mortality (OR:0.73, 95% CI [0.41-1.28]) and a significant reduction in 1-year mortality (OR:0.60, 95%CI [0.37-0.97]). In addition, peripheral cannulation reduced the risk of bleeding but increased the risk of limb ischemia and infection, with similar rates of stroke and need for renal replacement therapy.[85] However, a large single-center study ($n = 242$) not included in the meta-analysis demonstrated improved 3-month and 1-year survival with peripheral cannulation that remained significant after adjustment for donor and recipient variables, ischemic time, and transplant era.[24]

In cases of isolated RV dysfunction refractory to pharmacological therapy, the use of MCS and the choice of device depends on the setting of implantation.[86] Several experiences have been published to date, varying in device mechanism of action, level of support provided, cannulation, and associated adverse events and clinical outcomes.[86] The advent of less invasive, percutaneous MCS device options could overcome challenges related to surgical device implantation and may provide a safe and effective bridge to recovery.[86–88]

In patients with severe PGD after HTx, adequate ventricular recovery for weaning from MCS most commonly occurs within 5-6 days of cannulation.[89,90] However, the need for longer MCS support is not uncommon, and successful weaning after longer durations has been reported.[91] In this context, Connolly et al reported that

patients with severe PGD who had shorter ECMO runs (less than 4.5 days) had survival rates similar to those who did not require ECMO.[90] Even after successful weaning from MCS, residual subclinical dysfunction may persist, particularly in the RV, and monitoring is warranted.[92]

With mounting evidence on the inflammatory milieu in patients with severe PGD, immunomodulatory therapies such as induction therapy with anti-thymocyte globulin and IV immunoglobulin, as well as therapeutic plasma exchange (TPE), have been advocated as potential effective adjunctive therapies.[21,93–95] Manla et al reported that treating severe PGD-LV patients supported with VA-ECMO ($n = 42$) with TPE and ATG for 5 days followed by IV immunoglobulin for 2 days resulted in significantly improved survival at 30 days (78.1% vs 40%, $p = 0.007$) and at 1-year post-HTx (56.25% vs 30%, $p = 0.035$) compared to those who did not receive TPE.[94]

Intraoperative treatment of patients undergoing HTx using extracorporeal hemoadsorption, a blood purification technology capable of removing cytokines, chemokines, and various pharmacological agents, was found in a recent randomized controlled trial to improve hemodynamic stability and mitigate procalcitonin response post-transplant.[96] An ongoing trial [NCT05270902] at the Medical University of Vienna aims to investigate whether the use of hemoadsorption during CPB reduces circulating cytokine levels for the first 120 hours after HTx and whether this may mitigate the risk of PGD.[97]

For select patients who fail to recover, despite optimal MCS, and still demonstrate preserved end-organ function, urgent listing for redo transplantation may be considered.[2,75] However, outcomes in this population remain poor.[98] In a UNOS database analysis of redo-HTx from 2000 to 2020 ($n = 1,054$), patients with PGD represented 14% of the redo cases. Compared to other indications for redo-HTx, the PGD group had the second-lowest survival at 1 and 5 years, 70.6% and 56.7%, respectively.[98]

### 3.4.2. Breakout group discussion

Participants highlighted that the management of PGD is guided by the patient's PGD risk profile, perceived clinical severity, and anecdotal experiences with interventions that proved effective in recent cases at their center. Aside from inotropes/vasopressors and VA-ECMO, some of the participants thought levosimendan should be incorporated into severe PGD-LV management protocols, although this drug is not available in the US and other countries. A third of the participants supported the use of induction therapy, particularly with ATG, in cases of severe PGD. Participants noted that they are more likely to start ATG induction in patients with impaired renal function to delay CNI therapy but would avoid it in case of contraindication (e.g., infection, severe thrombocytopenia). Additionally, more than half of the participants suggested that TPE for 5 days post-HTx may be beneficial for patients with severe PGD but highlighted that prospective studies/trials are needed to strengthen available evidence. More than half of the participants thought redo-HTx should be an option for carefully selected refractory cases [after 5-7 days of ECMO support with no indication of recovery] but emphasized that these patients often have poor post-transplant survival.

### 3.4.3. Consensus statements

**#10.** If pharmacological therapy is insufficient to treat EGD, the decision and timing of MCS initiation, MCS device type, and implantation strategies depend mainly on patient clinical characteristics (risk factors, presentation timing, EGD-LV vs EGD-RV) and center experience.
**#11.** Therapeutic plasma exchange, in combination with immunomodulatory therapies, may offer a potential strategy to attenuate the inflammatory milieu in patients with severe EGD; however, further evidence is needed to support this approach.
**#12.** Heart re-transplantation may be indicated for carefully selected patients experiencing refractory severe EGD.

## 3.5. Question 5. How do we define (categorize) and distinguish secondary graft dysfunction? Should a severity scale be developed?

### 3.5.1. Background

Secondary Graft Dysfunction (SGD) was defined in the 2014 consensus document as graft dysfunction with an identifiable underlying cause.[2] Limited data is available on the incidence and outcomes of patients with SGD. Sabatino et al studied 518 transplants at 2 centers in Italy between 1999 and 2013 and reported an SGD incidence of 8.8%. Notably, the authors observed a downtrend in the incidence of SGD between 1999-2008 and

2009-2013, from 10% to 5.6%, which could be attributed to advancements in clinical practice, particularly in terms of patient selection and management of PH peri-operatively.[27] In multi-center registry data from the United Kingdom, including 450 heart transplants between 2012 and 2015, the incidence of SGD was estimated at 1.6%.[99] In a post-hoc analysis of 83 patients enrolled in a randomized clinical trial (Donor Simvastatin Treatment in HTx, NCT01160978) between 2010 and 2016, Holmström et al reported an SGD incidence of 10.8%.[60]

SGD occurs mainly due to surgical causes or PH and less frequently due to immunological causes, respiratory, iatrogenic, or other systemic causes.[2,100] Surgical complications resulting in SGD include occlusion of the coronary arteries, narrowed anastomosis, kinking of the pulmonary artery, and massive intraoperative hemorrhage, among others.[100] Obstruction of coronary arteries and narrowed anastomoses can result in RV and/or LV dysfunction, depending on the affected anatomical region. Pulmonary artery kinking leads to a significant increase in RV afterload, which could result in acute RV failure.[100] Intraoperative massive bleeding is common among patients undergoing HTx, especially in complicated cases (re-sternotomies, MCS explant, and coagulation disorders). In this setting, massive transfusion could result in volume overload, which may precipitate RV failure.[100] In the immediate postoperative period in the ICU, chest tube output is expected. However, an output of 1,500 mL within an hour or 200 mL/hr sustained over 4 hours may indicate active intrathoracic bleeding, which could be accompanied by hemodynamic instability.[101] Similarly, the sudden onset of hypotension accompanied by cardiac dysfunction may suggest blood accumulation in the pericardium.[101] Transesophageal echocardiographic assessment may be helpful in these cases, though tamponade remains a clinical diagnosis and cannot be ruled out by echocardiography.

PH is one of the more common causes of SGD. Elevated recipient pre-transplant pulmonary vascular resistance (PVR) is a significant risk factor for early post-transplant RV dysfunction and subsequent mortality, with an estimated 75% risk of RVF and 15% mortality in patients with pre-transplant PVR index > 6 WU/m$^2$, compared to 20% RVF risk in patients without increased PVR.[101–103] Thus, in all patients, particular attention should be given to continuous monitoring of pre-and post-operative pulmonary artery pressures.[101] In addition to inotropic agents, inhaled pulmonary vasodilators such as nitric oxide or prostacyclin analogs (e.g., epoprostenol) can be used to further reduce PVR, as they exert minimal systemic hypotensive effects.[23]

Hyperacute rejection is a rare complication that generally occurs within minutes to hours after reperfusion, wherein anti-ABO or anti-HLA antibodies bind to the donor heart, resulting in severe graft dysfunction.[100,101] The development and use of the prospective physical crossmatch, and subsequently the virtual crossmatch, has greatly reduced the frequency of this complication.[104] However, in patients with a negative prospective crossmatch who have been on the transplant waitlist for several weeks, preoperative blood transfusions (given after the stored blood sample date used for the prospective crossmatch) may lead to the development of anti-HLA antibodies, resulting in hyperacute rejection. In patients with suspected rejection, endomyocardial biopsy plays a critical role in identifying the underlying cause of SGD.

Table 5 summarizes suggested etiologies for SGD. Currently, there is no uniform classification or severity grading for SGD, and management mainly depends on addressing the underlying cause.

Data on the outcomes of SGD compared to PGD remain limited. In one study, PGD was associated with a slightly higher, albeit not statistically significant, rate of in-hospital mortality and need for urgent re-transplantation compared to SGD (37% vs 27%, $p = 0.2$).[27]

### 3.5.2. Breakout group discussion

Participants agreed that SGD is important to report. For this purpose, SGD is defined as LV (SGD-LV) and/or RV (SGD-RV) dysfunction with a known cause (e.g., surgical, PH, immunological, respiratory, and others), occurring within 72 hours after HTx, defined using hemodynamic and echocardiographic parameters (Table 5). It is important to comprehensively evaluate recipients for pre-transplant risk factors (e.g., elevated PVR, sensitization, previous cardiac surgery) for timely diagnosis and management of any potential contributors to SGD. Some participants suggested classifying SGD causes into reversible vs irreversible, while others suggested categorizing it based on etiology (immunological, surgical, etc). For highly complex surgical cases, participants emphasized the need for multidisciplinary perioperative planning with careful hemodynamic monitoring to mitigate the risk of SGD. Given the limited data available, participants agreed to hold off on proposing a grading scheme for SGD.

**Table 5** Definition and Causes of Secondary Graft Dysfunction

| | |
|---|---|
| Definition | SGD is defined as left ventricular (SGD-LV) and/or right ventricular (SGD-RV) dysfunction using below echocardiographic and hemodynamic parameters, occurring within 72 hours after HTx with a known underlying cause (see below).<br>*SGD-LV:*<br>Both of the following:<br>● LVEF ≤ 40%<br>● Hemodynamic compromise with RAP > 15 mm Hg, PCWP > 20 mm Hg, CI < 2.0 L/min/m$^2$, requiring inotropic support.<br>*SGD-RV:*<br>Both of the following:<br>● RVEF ≤ 35% and /or TAPSE < 1.6 cm<br>● Hemodynamics with RAP > 15 mm Hg, PCWP < 15 mm Hg, CI < 2.0 L/min/m$^2$, requiring inotropic support; TPG < 15 mm Hg and/or pulmonary artery systolic pressure < 50 mm Hg |
| Causes | Surgical:<br>● Technical: Kinking of the pulmonary artery, narrowing of the anastomosis, occlusion of coronary arteries<br>● Intraoperative hemorrhage leading to massive transfusions<br>● Cardiac tamponade |
| | Pulmonary hypertension:<br>● Pre-transplant pulmonary hypertension<br>● Intraoperative pulmonary hypertension (blood products, pulmonary anastomosis stenosis) |
| | Immunological:<br>● Hyperacute rejection (ABO incompatibility, sensitized patients)<br>● Acute rejection<br>● Allergy to medications |
| | Respiratory:<br>● Lung edema<br>● Acute respiratory distress syndrome |
| | Iatrogenic:<br>● Blocked intravenous drip lines<br>● Volume overload due to excessive administration<br>● Discontinuation of pulmonary vasodilators<br>● Rapid weaning of catecholamines |
| | Others:<br>● Vasoplegia<br>● Infection, Sepsis<br>● Acute renal failure<br>● Multi-system organ failure |

Abbreviations: CI, cardiac index; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; RVEF, right ventricular ejection fraction; SGD: secondary graft dysfunction; TAPSE, Tricuspid Annular Plane Systolic Excursion; TPG, transpulmonary pressure gradient.

### 3.5.3. Consensus statements

**#13.** SGD is defined as left ventricular (SGD-LV) and/or right ventricular (SGD-RV) dysfunction with a known cause (e.g., surgical, pulmonary hypertension, immunological, respiratory, or other) occurring within 72 hours after HTx, with further delineation to be established (Table 5).
**#14.** Comprehensive evaluation of recipient pre-transplant risk factors is essential for timely diagnosis and management of any potential contributors to SGD.
**#15.** In highly complex surgical cases, multidisciplinary perioperative planning, including careful hemodynamic monitoring, can help reduce the risk of SGD.

## 3.6. Question 6. Should vasoplegia be incorporated into PGD and/or secondary graft dysfunction? What criteria should be used?

### 3.6.1. Background

Patients undergoing HTx are at increased risk of developing refractory vasodilatory shock, known as vasoplegia.[19] Vasoplegia continues to confer significant morbidity and mortality and presents a clinical challenge to HTx teams due to the lack of a universally accepted definition and uncertainty regarding optimal management approaches for this condition.[105]

According to a meta-analysis by Kumar et al,[105] including 23 studies of 4,289 HTx patients, the reported incidence of vasoplegia was 28.7% (95% CI: 27.37%, 30.10%). Most of these studies defined vasoplegia as systemic hypotension (MAP < 70 mmHg) refractory to high doses of vasopressors, with low systemic vascular resistance (SVR < 800 dynes.sec.cm$^5$), typically with preserved cardiac function [CI ≥2.2 liter/min/m$^2$, and/or LVEF ≥ 50%] occurring within 48 hours of CPB.

The pathophysiology of vasoplegia remains unclear but is thought to involve a systemic inflammatory response to surgery, characterized by dysregulated cyclic guanosine monophosphate-nitic oxide pathways and inappropriate vascular relaxation.[106] The coexistence of vasoplegia and PGD is common,[18,107] as both conditions share several physiological pathways. For instance, if involved, the inflammatory milieu in PGD may lower SVR, contributing to vasoplegia.[2] Moreover, vasoplegia and the need for vasopressors may predispose to PGD. A study by Lim et al investigated the association between vasoplegia and delayed EGD (defined as the need for MCS use after admission to the ICU, within 24 hours post-transplant), using 2 hemodynamic parameters (SVRi and diastolic perfusion pressure) and norepinephrine equivalents (sum of vasopressor doses). They found that diastolic perfusion pressure and norepinephrine equivalents were significant predictors of delayed EGD.[20]

Several risk factors for vasoplegia have been identified in published studies,[18,105,108–111] including older age, male sex, higher body mass index, chronic liver disease, hypothyroidism, higher preoperative creatinine level, prior sternotomy, pre-HTx short-term MCS, durable LVAD or VA-ECMO, LVAD duration, pre-HTx medications (calcium channel blocker or amiodarone use), infection, longer CPB, and higher blood product transfusion requirement. In the meta-analysis by Kumar et al, those who developed post-HTx vasoplegia were almost 8 times more likely to require postoperative VA-ECMO, 4-fold more likely to require renal replacement therapy, more than 3-fold more likely to require reoperation for bleeding, and had 60% longer mechanical ventilation time. Patients who developed vasoplegia had significantly higher mortality at 30 days (14.5% vs 4.52%, $p < 0.001$) and at 1 year (18.62% vs 8.55%, $p < 0.001$).[105] Given the lack of a universal definition for vasoplegia, the interplay between PGD and vasoplegia remains challenging to delineate in clinical practice and underscores the need for further research to improve vasoplegia diagnostic and therapeutic strategies.

### 3.6.2. Breakout group discussion

Suggested criteria for defining vasoplegia included hypotension refractory to medical therapies and preserved CI with SVR < 800 dynes·sec·cm$^5$. Participants noted that the inotrope score is impractical for grading vasoplegia and recommended considering norepinephrine equivalents as a potential alternative.[109,112] Two clinical scenarios were described. First, EGD may be complicated by vasoplegia, which presents a clinical challenge and can lead to worse clinical outcomes. Second, in patients with vasoplegia and an initially well-functioning graft, any subsequent development of graft dysfunction should be evaluated, and vasoplegia should be considered a potential contributor to SGD in this case (Table 5). The discussants emphasized the need for further research to deepen our understanding of vasoplegia pathophysiology and its interplay with EGD.

### 3.6.3. Consensus statements

**#16.** In the context of graft dysfunction and vasoplegia, 2 clinical scenarios can be identified:

1) EGD may be complicated by vasoplegia, which can worsen clinical outcomes and posesignificant management challenges.

2) In patients with vasoplegia and an initially well-functioning graft, the onset of graft dysfunction should be assessed with consideration of vasoplegia as a potential contributorto SGD.

## 4. SUMMARY OF THE CONSENSUS DOCUMENT

The 2024 Consensus Conference provided an overview of the current understanding of graft dysfunction within the first 72 hours after HTx. Conference participants recommended changing the terminology of “PGD” to “EGD” and introduced a revised severity scale of EGD correlated with the prior scale in order to maintain data relevance and enable comparisons across eras. Immediate presentation of EGD vs delayed presentation within the 24-hour period was added to the definition, as they have different prognostic outcomes. The participants shed light on recently identified donor, recipient, and procedural risk factors and biomarkers of EGD and emphasized the need

**Table 6** Summary of Consensus Conference Recommendations

**#1.** Graft dysfunction within the first 72 hours after transplant is to be further categorized into cases with a discernible cause (secondary graft dysfunction) and those with an unknown cause (Figure 1).
**#2.** Graft dysfunction with unknown cause should be further classified into early graft dysfunction < 24 hours (EGD) which replaces the previous term of PGD; or subsequent graft dysfunction Dysfunction at 24-72 hours post-HTx (sEGD).
**#3.** EGD and sEGD to be further classified into LV (Left ventricular or biventricular dysfunction) or RV (Isolated right ventricular dysfunction) (Figure 1).
**#4.** Severe EGD-LV should be further categorized based on the timing of presentation into Immediate Presentation (EGD-LVip, failure to wean from cardiopulmonary bypass) or Delayed Presentation (EGD-LVdp, occurring after successful weaning from cardiopulmonary bypass), as this timing appears to hold significant prognostic value (Figure 1).
**#5.** EGD-LV and EGD-RV are to be classified into 2 grades: non-severe or severe, based on the need to initiate MCS for cardiac dysfunction after transplantation. The inotrope score will no longer be used for grading the severity of EGD (Table 2).
**#6.** Evaluation of donor, procedural, and recipient EGD risk factors is essential to guide EGD prevention and management strategies. Avoiding high-risk combinations and addressing modifiable risk factors, when possible, are likely to improve outcomes.
**#7.** Building registries with comprehensive data on pre-transplant recipient and donor characteristics, preservation and management strategies, and associated clinical outcomes of patients with EGD and incorporating artificial intelligence and machine learning approaches may help identify risk factors, refine definitions, and serve as the foundation for rigorous clinical trials.
**#8.** The use of novel organ preservation and transportation technologies may mitigate the risk of EGD development.
**#9.** Discontinuation of amiodarone in patients listed for HTx and holding RAAS inhibitors prior to surgery may reduce the risk of EGD.
**#10.** If pharmacological therapy is insufficient to treat EGD, the decision and timing of MCS initiation, MCS device type, and implantation strategies depend mainly on patient clinical characteristics (risk factors, presentation timing, EGD-LV vs. EGD-RV) and center experience.
**#11.** Theraputic plasma exchange, in combination with immunomodulatory therapies, may offer a potential strategy to attenuate the inflammatory milieu in patients with severe EGD; however, further evidence is needed to support this approach.
**#12.** Heart re-transplantation may be indicated for carefully selected patients experiencing refractory severe EGD.
**#13.** SGD is defined as left ventricular (SGD-LV) and/or right ventricular (SGD-RV) dysfunction with a known cause (e.g., surgical, pulmonary hypertension, immunological, respiratory, or other) occurring within 72 hours after HTx, with further delineation to be established (Table 5).
**#14.** Comprehensive evaluation of recipient pre-transplant risk factors is essential for timely diagnosis and management of any potential contributors to SGD.
**#15.** In highly complex surgical cases, multidisciplinary perioperative planning, including careful hemodynamic monitoring, can help reduce the risk of SGD.
**#16.** In the context of graft dysfunction and vasoplegia, 2 clinical scenarios can be identified:
1) EGD may be complicated by vasoplegia, which can worsen clinical outcomes and pose significant management challenges.
2) In patients with vasoplegia and an initially well-functioning graft, the onset of graft dysfunction should be assessed with consideration of vasoplegia as a potential contributor to secondary graft dysfunction.

for comprehensive registries incorporating artificial intelligence and machine learning approaches to help identify predictive factors and to refine definitions of EGD. Discussants delved into current EGD preventive strategies, including perioperative risk optimization, novel organ preservation and transportation technologies, and potential therapeutic approaches. Causes and definition of SGD post-HTx were also explored. Participants finally elaborated on the interplay between EGD and vasoplegia. We hope the results of this consensus conference will provide a more standardized pathway for the prevention, diagnosis, and management of graft dysfunction after HTx and pave the way for future studies. The consensus conference statements are summarized in Table 6.

## DISCLOSURE STATEMENT

Jon Kobashigawa: received research grants from CareDx Inc., Sanofi-Genzyme, and CSL-Behringer. Andreas Zuckermann reports speaker honoraria and advisory roles with Paragonix Technologies, Therakos (Mallinckrodt), Takeda, and Sanofi; serves as Local Principal Investigator for the XVIVO NHIP2019 study and the Cytotect NIS021 study (Biotest); is the European Principal Investigator for the GUARDIAN Registry (Paragonix); has received institutional (non-personal) study support from Biotest (NIS021); participates in advisory boards for Sanofi and Therakos; and serves as an independent adjudicator for primary graft dysfunction (PGD) for the XVIVO study. Luciano Potena: received consulting fees from Biotest, Roche diagnostics, received honorarium from Takeda, Abbott, Biotest, and holds a leadership position at ESOT. Abbas Ardehali was an investigator in the Transmedics ESLP trials. Fardad Esmailian received a research grant from TransMedics. Maryjane Farr serves on TransMedics Inc., Natera, and the data safety monitoring board and also serves as Co-Chair, Transthoracic and Critical Care Community of Practice,

American Society of Transplantation. Shelley Hall received consulting fees from CVRx, Abbott, CareDx, and Honoria from Natera and serves as a board member for the American Society of Transplant. Eileen Hsich received NIH, NHLBI grant support R01HL164405. Yasbanoo Moayedi received funding from the AMO–UHN–Sinai Innovation Fund and ACT—Accelerating Clinical Trials. Peter MacDonald received consulting fees from AstraZeneca, Boehringer, and Novartis, and honoraria from Astellas, Abbott, Boehringer, as well as support to attend the Indian Society for Heart and Lung Transplantation and the Congress of the Asian Society of Transplantation meeting, and received equipment support from Transmedics and XVIVO, has stock in Infensa Bioscience and serves on the data safety Monitoring Board for Eli Lilly. All other authors have no conflicts of interest to disclose.

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## APPENDIX. : PARTICIPANTS IN THE CONSENSUS CONFERENCE

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# APPENDIX A. SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.healun.2025.12.029.

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