




Review

# Primary Graft Dysfunction Following Heart Transplantation: A Modern Review of Primary Graft Dysfunction

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Academic Editor: Massimo Bonacchi

Submitted: 17 March 2025 Revised: 8 May 2025 Accepted: 5 September 2025 Published: 27 October 2025

## Abstract

Primary graft dysfunction (PGD) represents a poor prognostic outcome for patients undergoing orthotopic heart transplantation (OHT). The risk factors associated with PGD are multifactorial and complex, encompassing factors related to the donor, recipient, and preservation. The early expansion of donation after circulatory death (DCD) donors has also resulted in an increased incidence of PGD. This paper aims to review the pertinent literature on the risk factors, patient outcomes, and trends of PGD post-OHT. Further discussion regarding PGD following DCD from an OHT, the treatment of PGD, and current efforts to decrease PGD are also explored.

**Keywords:** heart transplantation; primary graft dysfunction; organ preservation; orthotopic heart transplantation; donation after circulatory death

## 1. Introduction

Orthotopic heart transplantation (OHT) is the gold standard for patients with end-stage heart failure refractory to medical management. The first human heart transplant (HT) occurred in 1967, performed by Christiaan Barnard, using a donation after circulatory death (DCD) donor [1]. Subsequent breakthroughs in immunosuppression, following the introduction of cyclosporin, allowed for improvements in treatment to prevent acute and chronic transplant rejection [2]. Currently, more than 5000 HTs occur annually worldwide, with approximately 4000 taking place in the United States, representing a 53% increase from 2011. Median survival post-OHT is reported by the International Society for Heart and Lung Transplantation (ISHLT) to be 11.9 years [3,4]. However, an estimated 50,000 patients remain on the waitlist. There has been a steady bottleneck in the number of donors per year, although the number of donors has increased and the number of hearts procured after circulatory death has grown since 2015 [5]. Despite advances in the care of these patients, primary graft dysfunction (PGD) remains a fatal complication.

Historically, PGD has been poorly defined. In 2014, the ISHLT released a consensus statement that required the diagnosis of PGD to be made within the first 24 hours after transplantation and divided PGD into left ventricular (PGD LV) and right ventricular (PGD RV) subtypes. Importantly, PGD LV was defined as mild, moderate, or severe based on ejection fraction, hemodynamic criteria, and need for mechanical support. Severe PGD was defined as the need for LV or biventricular mechanical support, excluding an intra-aortic balloon pump (IABP). The statement also clarified

that PGD had to be in the absence of a known reason for secondary graft dysfunction (e.g., pulmonary hypertension, hyperacute rejection) [6]. The purpose of this review is to provide a modern overview of the risk factors associated with PGD, explore the impact of DCD donation on PGD, review the treatment options for PGD, and discuss current efforts to mitigate PGD.

## 2. Risk Factors for Developing PGD

PGD is thought to result from the donor heart being subjected to insults between donor, procurement, and recipient-specific factors (Table 1, Ref. [6]). The physiological events after donor brain death have been known to lead to the release of proinflammatory mediators and impair myocardial contractility [7]. Donor hearts are susceptible to both cold and warm ischemic periods. Historically, during transportation, these hearts were stored in a cold solution on ice. While cold storage slows cellular metabolism, some ischemic damage still occurs. Additionally, there is a period of warm ischemia when the heart is implanted into the recipient. Moreover, the release of the recipient cross-clamp and reperfusion of the donor heart result in the formation of oxygen-derived free radicals, which lead to cell death and contribute to reperfusion injury [8].

### 2.1 Donor Age

In terms of donor-specific factors, older donors are less tolerant to prolonged ischemia. Avtaar Singh *et al.* [9] highlighted a ~20% increase in the incidence of PGD for each decade increment. This finding was also noted by Loebe *et al.* and colleagues [10]. A systematic analysis



**Table 1. Risk factors associated with primary graft dysfunction.**

Donor factors	Recipient factors	Procurement/preservation/procedural factors
Older age	Older age	Long ischemic time
Female donor:male recipient mismatch	Increased weight	Center volume/experience
Undersized donor (PHM >30%)	Mechanical support (ECMO, VAD)	Long cardiopulmonary bypass time
Comorbidities: diabetes, hypertension	Redo-sternotomy	Multiorgan transplant
High inotropy requirements	Ventilator dependence	
Cause of death: intracranial hemorrhage	Amiodarone use	
Left ventricular hypertrophy	Comorbidities	
Cardiac dysfunction	Retransplantation	
DCD donor	Congenital heart disease	
	Infection	

Adopted from the ISHLT 2014 PGD Guidelines [6]. PHM, predicted heart mass; ECMO, extracorporeal membrane oxygenation; VAD, ventricular assist device.

of 178,031 donors by the United Network for Organ Sharing (UNOS) divided ischemia times into three categories: limited (0–3.49 hours), prolonged (3.50–6.24 hours), and extended ( $\geq 6.25$  hours). Between the donor age groups of 20–33 and those aged 34 years or older, the extended ischemic times were associated with approximately a 14% increase in the incidence of 5-year mortality [11].

### 2.2 Left Ventricular Hypertrophy

The impact of ischemia on donors with left ventricular hypertrophy (LVH) has also been investigated. Currently, almost half of all transplanted hearts demonstrate a degree of LVH. An analysis utilizing the UNOS database showcased an increased risk of death amongst recipients of donor allografts with moderate–severe LVH and an ischemic time  $\geq 4$  hours (hazard ratio (HR) 2.23, 95% confidence interval (CI) 1.01–4.93;  $p = 0.04$ ) [12]. There was no correlation between LVH and mortality amongst younger deceased brain dead (DBD) donors. However, a subgroup analysis of donors with LVH and ages  $>55$  years showed a markedly increased risk of death (mild LVH: HR 6.66, 95% CI 1.43–30.91;  $p = 0.01$ ; moderate–severe LVH: HR 6.47, 95% CI 0.58–71.37;  $p = 0.12$ ) [12]. This is important as older donors with LVH may not be able to withstand prolonged periods of ischemia, which should be considered when evaluating potential donors and estimating organ ischemic time [13]. The impact of donor LVH in DCD donors currently remains unknown.

### 2.3 Donor Inotropy

Donor inotropic use is another important factor associated with PGD [14,15]. A multivariate systemic analysis suggested that high-dose donor inotropic support was the strongest determinant of PGD (odds ratio (OR): 7.5;  $p = 0.01$ ) [16].

### 2.4 Cause of Death for Donor

The cause of death of the donor has also been considered as another predicting factor for the subsequent de-

velopment of PGD. Intracranial hemorrhage and the subsequent catecholamine surge have been proposed as a reason for graft dysfunction [9]. Prior work has suggested donor intracranial bleeding (ICB) as the cause of death that represents an independent predictor of recipient mortality (adjusted HR 2.02, 95% CI 1.27–3.40;  $p < 0.0001$ ). Compared with donors that died from trauma, the ICB group had an increased incidence of post-transplant graft dysfunction during the first week of transplant (10% vs. 3%;  $p = 0.007$ ), and a higher incidence of interstitial myocardial fibrosis on their endomyocardial biopsies within 4 weeks of transplant (21% vs. 9%;  $p = 0.001$ ) [17].

### 2.5 Sex Matching

A large retrospective cohort study examined sex mismatching between donors and recipients. Unadjusted survival rates were worse in female recipients compared to males (HR: 1.09;  $p = 0.02$ ). However, survival differences among female recipients were not associated with the sex of the donor. Male recipients of female donor hearts demonstrated worse survival than male recipients of male donors (1-year HR: 1.28;  $p = 0.02$ ). Female patients showed no major difference in survival when receiving their graft from a male or female donor [18]. Although the exact mechanism remains unclear, the potential role of H-Y minor histocompatibility antigens has been implicated. Several hematopoietic stem cell studies have shown an increased relapse rate in patients undergoing stem cell transplants in female donor/male recipient cohorts in cases of cancer [19]. These findings suggest that a gender mismatch may play a significant role in understanding the root causes of various graft-versus-host disease pathologies.

### 2.6 Size Mismatch

Previous studies have indicated that the predicted heart mass (PHM) may provide better size matching in cardiac transplantation compared to total body weight (TBW) [18]. PGD was associated with an under-sizing of  $>30\%$  if performed according to the PHM ( $p = 0.007$ ), but not if per-

formed using the TBW ( $p = 0.49$ ). One-year survival rates were not significantly different between groups (log-rank,  $p > 0.8$ ). Multivariate analysis revealed that under-sizing donor hearts using the PHM, but not the TBW, was predictive of moderate to severe PGD (OR 3.3, 95% CI 1.3–8.6) [20].

### 2.7 Recipient Age

In terms of recipient-associated risk factors, age also represents an important predictor of PGD development post-heart transplantation. A recipient age of  $>60$  years has been suggested as a strong predictor for PGD (OR: 2.11;  $p = 0.01$ ) [14]. The higher rates of infection, hypertension, and diabetes in older recipients have been elucidated as a potential reason for their poor prognosis post-OHT [21,22].

### 2.8 Presence of Mechanical Support

Due to advancements in medical treatments and a consistently limited supply of organ donors, patients waiting for HTs are increasingly older and have a higher prevalence of comorbid conditions such as obesity, diabetes, hypertension, and renal disease. As wait times continue to increase, more patients are becoming bridged to transplant (BTT) using continuous flow left ventricular assist devices (CF-LVADs). Patients supported with a durable LVAD for more than one year before heart transplantation have been shown to experience longer durations of hospital stays after the transplant, greater PGD, and decreased survival rates at the three-year post-transplant follow-up [23].

The use of extracorporeal life support (ECLS) to support decompensated patients before heart transplantation has demonstrated modest outcomes, with varying results reported in the literature. In a study conducted by Chung and colleagues [24] involving patients who were initiated on venoarterial extracorporeal membrane oxygenation (VA-ECMO) to BTT, it was found that 44% of patients were successfully bridged. The analysis identified several independent predictors of unsuccessful bridging, including being over 50 years of age, the necessity for cardiopulmonary resuscitation before ECMO, and a sequential organ failure assessment (SOFA) score  $>10$  at the time of ECMO initiation [24].

A recent retrospective analysis from the French National Registry (CRISTAL) further examined this issue. This analysis compared 80 patients classified on a “high-urgency list” who received ECMO support as a BTT with 866 patients who did not require ECMO. The findings indicated that the one-year overall survival rate for candidates on ECMO was 52.2%, in contrast to 75.5% for those who did not require ECMO support. Additionally, the one-year post-transplant survival rate was 70% within the VA-ECMO group, compared to 81% in the control group. The authors concluded that while transplantation provides a survival benefit for patients on VA-ECMO, post-transplant survival remains lower than that of patients who did not require

ECMO. Finally, the authors suggested that, under certain circumstances, ECMO can be used as a BTT [25].

Takeda and colleagues [26] from Columbia University analyzed patients needing mechanical support for severe PGD after a HT. Out of 597 HT patients, 44 (7.4%) developed severe PGD. Meanwhile, within 24 hours post-transplant, 17 patients received a continuous-flow external ventricular assist device (VAD), while 27 patients were treated with VA-ECMO. Those on VAD support had longer support times, higher rates of major bleeding requiring chest re-exploration, and a higher incidence of renal failure needing renal replacement therapy. In-hospital mortality was 41% for the patients with a VAD and 19% for those on VA-ECMO. Of the patients, 10 (59%) were weaned off the VAD, while 24 (89%) were weaned from VA-ECMO after recovering the graft function. The three-year survival rates were 41% for the VAD group and 66% for the VA-ECMO group, suggesting that VA-ECMO support offers better outcomes for severe PGD.

### 2.9 Redo Sternotomy

Patients requiring redo sternotomy have also been associated with a higher incidence of PGD [27,28]. Recipients with a history of sternotomy were generally older, predominantly male, and had a higher body mass index (BMI). This group also presented a greater prevalence of UNOS 1A status under the old allocation system, as well as ischemic cardiomyopathy. Additionally, these patients faced significantly longer waitlist times compared to those without prior sternotomy (34.5 days vs. 19 days). Patients in this group showed markedly higher rates of mild to severe PGD versus those without sternotomy (32% vs. 18%) as well as a reduced one-year post-transplant survival [27]. Moreover, prior sternotomy has been associated with the need for additional blood transfusions and a higher incidence of post-operative complications, such as pneumonia and wound infections, leading to extended hospital stays [26].

### 2.10 Recipient Amiodarone Use

Amiodarone use is a known risk factor for PGD amongst the transplant community and was reinforced by a recent meta-analysis of 26,268 patients [28]. The group exposed to amiodarone before heart transplantation exhibited a higher incidence of PGD compared to those who had not received amiodarone (4.42% vs. 2.98%). The 30-day mortality was also higher in the amiodarone-exposed cohort (4.53% vs. 3.33%) [29].

A separate triple-group study suggested that patients who received amiodarone and continued the treatment up to transplantation had greater odds of developing severe PGD compared to those who had not been treated with amiodarone in the six months before OHT. Patients who had stopped amiodarone treatment for more than six months before transplantation showed no significant difference in their likelihood of developing severe PGD compared to

those who received no amiodarone treatment before OHT. These findings support the current practice of discontinuing amiodarone to reduce the risk of severe primary graft dysfunction [30].

Additionally, a correlation has been identified between the dose of amiodarone administered before OHT and the subsequent development of PGD. Continuous analysis revealed that for each 100 mg increase in the amiodarone dose on the day of the OHT, there was a 55% increase in the odds of developing severe PGD, after adjusting for the presence of a VAD, donor left ventricular ejection fraction (LVEF), and ischemic time ( $p < 0.001$ ). The cumulative amiodarone dose in the six months preceding the OHT also influenced outcomes, with an 18,300 mg increase in dosage correlating with a 67% increase in the odds of developing severe PGD [31]. In addition to dosage, the duration of amiodarone treatment can affect prognostic outcomes, with a three-fold increase in the development of PGD for recipients who had been on amiodarone for more than four weeks [32].

### 2.11 Predicting PGD

An algorithmic scoring model has been developed to improve the predictions of PGD. The model was developed using six multivariate risk factors for PGD: right atrial pressure  $\geq 10$  mmHg, recipient age  $>60$  years, diabetes mellitus, inotrope dependence, donor age  $>30$  years, and length of ischemic time  $>240$  minutes, referred to as the right atrial pressure, age, diabetes, ischemic time (RADIAL) score. Analysis of isolated right ventricular failure revealed similar predictors. The RADIAL score assigns 1 point for each risk factor present after OHT. The incidence of primary graft failure significantly increased with a higher RADIAL score ( $p < 0.001$ ). The actual and predicted rates of PGD incidence for different RADIAL subgroups showed good correlation (C-statistic 0.74) [33]. This model was later validated in a separate study in Spain [34].

### 2.12 Longer Ischemia Times

It is well documented that donor heart ischemic time influences transplant outcomes and subsequent PGD development [35–37]. Historically, an ischemia time  $\geq 4$  hours has been associated with an increased risk for PGD (OR 10.3;  $p = 0.007$ ) and mortality [36]. Another UNOS study, including 36,145 patients, demonstrated that an ischemic time  $\geq 3$  hours increased the incidence of death from PGD (1.8% vs. 1.2%;  $p < 0.001$ ) [37].

## 3. Primary Graft Dysfunction in Donation After Circulatory Death (DCD) Donors: Early Results

As demands for transplantation have increased in recent years, donation parameters have also been expanded to meet the growing need for organs. Consequently, donation after circulatory death (DCD) is becoming more preva-

lent [38]. Published studies have demonstrated a nearly 7% increase in the use of DCD donors for heart transplantation between 2019 and 2021 [39]. Although the adoption of DCD transplantation has expanded the donor pool, early results suggest a higher risk of PGD. The incidence of moderate or severe PGD following OHT was reported as 34% in DCD donors compared to 23% in DBD donors [40]. A randomized clinical trial comparing DCD to DBD OHT also found an increased incidence of moderate to severe PGD in DCD donors (22% vs. 10%). However, there was no difference in the 6-month survival between the groups (94% vs. 90%) [41].

For the DCD donation, there is a period of functional warm ischemia after withdrawal of donor lifesaving support when the heart is no longer being adequately perfused [42]. During the warm ischemic time (WIT), cellular metabolism continues, leading to the depletion of cellular resources and nutrients [43]. Previous work has shown increased inflammation, myocardial edema, and injury in DCD versus DBD donor hearts [44]. The cellular swelling and damage sustained due to the WIT can increase the likelihood of later developing PGD [45]. Additionally, although a WIT period is unavoidable in DCD transplantation, the amount of WIT a donor heart can tolerate is an area of active interest. According to the current literature, no significant cellular damage is observed within ten minutes of circulatory arrest [42]. However, in the following period, DCD hearts demonstrated significant increases in activation of apoptotic death processes, as measured by caspase 3 and 7 activity [42]. Furthermore, a decrease in the activity of mitochondrial complexes II and IV has been shown to occur ten minutes after circulatory arrest, suggesting severe mitochondrial dysfunction, along with impaired contractility of cardiac muscle fibers [42].

Recent studies on DCD and the WIT have demonstrated that, although heart functionality is best preserved at WITs below ten minutes, the WITs up to 30 minutes have shown no adverse early outcomes in patients [46]. Although DCD cardiac output begins to decline after a WIT of 10 minutes, the heart can recover to full capacity if the WIT is kept below 30 minutes [46]. Furthermore, flushing donor organs with a supplemented vitamin C solution has been shown to preserve their functionality further and allow them to achieve full recovery, especially when the WIT begins to approach 30 minutes [46]. Meanwhile, extending the WIT to 40 minutes, despite flushing with supplemented vitamin C solutions, demonstrated only partial recovery of the organ [46]. Long-term outcomes of DCD OHT remain unknown.

For the DCD donation, there are two main types of organ procurement: normothermic region perfusion (NRP) and direct procurement and preservation (DPP); NRP involves reperfusion of the organ in the donor before procurement while DPP requires procurement of the organ, followed by resuscitation of the donor heart, on the Organ

Care System (OCS) (Transmedics, Andover, MA, USA). The OCS device supplies oxygenated blood to the coronary arteries at rest. Despite the differential treatment of the organs, studies have observed no significant differences in the likelihood of severe PGD at 24 hours between the techniques (DPP: 9.4% vs. NRP: 9.7%) [47].

#### 4. Treatment of Primary Graft Dysfunction

As PGD is one of the strongest predictors of mortality following heart transplantation, prompt diagnosis and management are essential. Young and colleagues [48] reported one-month mortality post-HT to be as high as 43%.

Notably, inotropic agents are effective for mild to moderate PGD. Administration of inotropic agents can re-establish cardiac contractility and graft stability [49]. In particular, levosimendan, when administered with the standard regimen of immunosuppressive medications, has been shown to improve PGD outcomes. Patients who received levosimendan showed improved cardiac output, ejection fraction, and mean arterial pressure. The need for inotropic support was eliminated in 80% of patients within 48 hours of levosimendan administration [50]. Additionally, studies have shown that steroid pulse therapy may be beneficial in limiting the activation of the immune system in cases of PGD [48]. When combined with plasmapheresis in patients with mild to moderate PGD, steroid pulse therapy has been shown to improve both cardiac contractility and overall outcomes in over 70% of patients [51,52].

For patients suffering specifically from moderate PGD, in-hospital mortality rates have been reported to be approximately 12% [49]. Intra-aortic balloon pump (IABP) placement for the treatment of moderate PGD provides temporary mechanical support that helps to increase perfusion of the transplanted graft along with cardiac output [53]. Patients suffering from moderate PGD who receive an IABP have similar long-term survival and complication rates as patients who did not develop PGD following OHT [54].

Patients suffering from severe PGD require more intensive support, often requiring ECMO. Initiation of ECMO has been shown to improve outcomes beyond those of patients who received biventricular assist devices. Patients who received ECMO for PGD experienced fewer events of bleeding or complications compared to those who received VADs [14]. While survival has been reported to be inferior in patients requiring ECMO for PGD, one study suggested that patients who needed a short duration of ECMO support (<108 hours) had similar long-term survival to patients not requiring ECMO [55]. In addition to the implementation of VA ECMO, literature on PGD has shown that the combination of VA ECMO and plasmapheresis leads to significantly reduced patient mortality in those who develop PGD [56]. Due to the potential benefits of plasmapheresis that were previously demonstrated in liver transplantation, it was applied to the treatment of PGD

patients following OHT. Thirty-day survival rates for a cohort of 42 patients with severe PGD who received plasmapheresis were approximately 80%, compared to 40% for patients with severe PGD who did not receive plasmapheresis [56,57]. Notably, plasmapheresis is used in PGD because it is believed to be effective in removing soluble inflammatory molecules, thereby mitigating the extent and severity of inflammation associated with PGD [58]. Retransplantation is an option for severe PGD refractory to medical management, although the current literature on retransplantation remains limited. One single institution study revealed a median survival of 0.2 years for all patients undergoing retransplantation within 1 year of a primary transplant (all patients underwent retransplant within 1 year for PGD) [59]. Another analysis of the UNOS database found a median survival of 1.6 years for patients undergoing retransplant within the first 90 days [60]. Nonetheless, the challenge remains in selecting the appropriate patients for retransplantation and determining the optimal timing for these procedures.

#### 5. Efforts to Decrease Primary Graft Dysfunction

Continued efforts to identify patient, donor, and preservation risk factors that contribute to PGD after OHT are needed. In the United States, the Organ Procurement and Transplantation Network (OPTN) has suggested adding new data elements to the Transplant Recipient Registration (TRR) form to improve reporting and ultimately reduce the incidence of PGD [61]. Additional data elements that have been suggested for inclusion include granular perioperative hemodynamics, descriptive imaging findings, the need to return to the operating room for mediastinal bleeding, perioperative inotropic/vasoactive drug use and dosing, and blood product administration [61].

The impact of cardioplegia on PGD has also been analyzed. Administration of blood cardioplegia every 20 minutes during implantation, which is leucocyte-depleted by 40  $\mu$  inline filtration, has been suggested to decrease PGD [61]. According to Cobert *et al.* [62], hypothermic machine perfusion has the potential to improve heart preservation by extending the ischemic interval of the donor. Machine perfusion performed either by the retrograde or antegrade technique can help support myocardial metabolism over an extended duration. Both methods enable the heart to continue consuming oxygen while maintaining normal energy phosphate levels [62].

Preservation conditions of the donor heart can greatly decrease the incidence of primary graft dysfunction. Traditionally, the unpredictable thermal fluctuations associated with the use of ice coolers had the potential to cause cellular damage to the donor heart during transportation. The SherpaPak Cardiac Transport System (Paragonix Technologies, Waltham, MA, USA) has been designed to maintain the preservation environment of the donor heart by controlling

the temperature between 4 °C and 8 °C. When compared to traditional ice storage, controlled hypothermic preservation has led to a reduction in severe PGD (10.4% vs. 6.5%) [63].

As DCD continues to expand, techniques associated with preservation and implantation are currently evolving. In an attempt to decrease ischemia-reperfusion injury, Krishnan *et al.* [64] have described beating heart transplantation—an implantation technique that includes uninterrupted coronary perfusion during implantation. This new technique helps avoid the second cardioplegic arrest that is often needed for DCD heart transplantation when the OCS device is utilized. In this study, ten patients underwent DCD heart transplantation with this implantation technique, with 100% hospital survival and no cases of PGD [64]. Overall, as the field of heart transplantation continues to evolve, the preservation and implantation techniques should be considered in conjunction with donor and recipient risk factors. Thus, a combination of strategies may be necessary to reduce PGD.

## 6. Conclusion

Despite recent significant advances in heart transplantation, PGD remains a significant burden and contributes to early post-transplant mortality. The impact of specific donor, procurement, preservation, and recipient factors has been extensively reported. In cases of severe PGD, ECMO remains the mainstay of treatment. Although the adoption of DCD transplantation has expanded the donor pool, early results suggest a higher risk of PGD in comparison to DBD donors. Advances in data reporting, preservation technology, and implantation technique offer promise to improve PGD as the field continues to expand the boundaries to meet the growing demand for transplantation.

## Author Contributions

BF, JT, TS, ADC, and KSH contributed to the design of this work. JT, MM, and MDJM contributed to the interpretation of data. JT analyzed the data. JT, MM, and MDJM drafted the work. BF, JT, TS, ADC, and KSH revised critically for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

Not applicable.

## Acknowledgment

Not applicable.

## Funding

This research received no external funding.

## Conflict of Interest

The authors declare no conflict of interest. Tadahisa Sugiura is serving as one of the Editorial Board members of this journal. We declare that Tadahisa Sugiura was not involved in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Massimo Bonacchi.

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