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ORIGINAL PAPER

Mechanical circulatory support with Impella versus intra-aortic balloon pump or medical treatment in cardiogenic shock—a critical appraisal of current data

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Abstract

Aims Patients suffering from cardiogenic shock (CS) have a high mortality and morbidity. The Impella percutaneous left-ventricular assist device (LVAD) decreases LV preload, increases cardiac output, and improves coronary blood flow. We aimed to review and meta-analyze available data comparing Impella versus intra-aortic pump (IABP) counterpulsation or medical treatment in CS due to acute myocardial infarction or post-cardiac arrest.

Methods and results Study-level data were analyzed. Heterogeneity was assessed using the I^2 statistic. Risk rates were calculated and obtained using a random-effects model (DerSimonian and Laird). Four studies were found suitable for the final analysis, including 588 patients. Primary endpoint was short-term mortality (in-hospital or 30-day mortality).

In a meta-analysis of four studies comparing Impella versus control, Impella was not associated with improved short-term mortality (in-hospital or 30-day mortality; RR 0.84; 95% CI 0.57–1.24; $p=0.38$; I^2 55%). Stroke risk was not increased (RR 1.00; 95% CI 0.36–2.81; $p=1.00$; $I^2$2 0%), but risk for major bleeding (RR 3.11 95% CI 1.50–6.44; $p=0.002$; I^2 0%) and peripheral ischemia complications (RR 2.58; 95% CI 1.24–5.34; $p=0.01$; I^2 0%) were increased in the Impella group.

Conclusion In patients suffering from severe CS due to AMI, the use of Impella is not associated with improved short-time survival but with higher complications rates compared to IABP and medical treatment. Better patient selection avoiding Impella implantation in futile situations or in possible lower risk CS might be necessary to elucidate possible advantages of Impella in future studies.

Keywords Impella · IABP · Mechanical support system · Cardiogenic shock · Emergency treatment

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Introduction

Cardiogenic shock (CS) is defined as hypotension due to low cardiac output leading to tissue hypoperfusion and hypoxia. Patients suffering from CS have a high mortality and survivors suffer from high morbidity [1, 2]. The two major causes of CS constitute acute myocardial infarction (AMI–CS) and cardiac arrest (CA–CS) [3]. Medical treatment consisting of inotropes, fluid resuscitation, and catecholamines aiming to improve organ perfusion and cardiac output failed to significantly improve outcomes in these patients [1, 4].

Percutaneous mechanical support devices (pMCS) were developed to improve hemodynamics and reduce mortality in CS [5–8]. The first device evaluated was the intra-aortic balloon pump (IABP) which augments cardiac function and several studies indicated left-ventricular (LV) unloading and improved flow in the coronaries [9]. Still, IABP did not show

improved survival versus medical treatment in AMI–CS when evaluated in the randomized IABP-SHOCK II trial and its use declined [10, 11].

This is likely attributed to the limited hemodynamic effect of IABP support in patients with low cardiac output. More powerful devices such as the Impella (Abiomed, Danvers, Massachusetts) were increasingly applied [8, 12, 13]. The Impella is a micro-axial flow pump actively delivering blood from the LV into the ascending aorta and can augment cardiac output. Depending on the specific device, Impella provides a flow of up to 5 L/min, and it may increase mean arterial pressure and may reduce myocardial work [14]. Experimental studies suggested LV unloading, an increase in cardiac output, and improved blood flow in the coronary arteries in Impella patients [15].

Both AMI–CS and CA–CS patients suffer from low cardiac output, systemic hypoperfusion, ischemia/reperfusion syndrome, and, hence, multiorgan failure leading to death. While, specifically in AMI–CS, early reperfusion is crucial, in both conditions, LV unloading and an increase in cardiac output using pMCS might lead to improvements in outcome. Impella was successfully implanted in both AMI–CS and CA–CS. Recently, a large study reported results from a matched cohort comparing Impella versus patients from IABP-SHOCK II (consisting of 36% of CS patients with CA due to AMI) receiving either IABP or medical treatment [16]. We, therefore, aimed to review and meta-analyze available data comparing Impella versus IABP or medical treatment in CS both due to AMI or CA.

Methods

This study was performed according to established methods and in adherence to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement for reporting systematic reviews and meta-analyses in health care interventions [17, 18].

Literature search

The PRISMA flowchart illustrating publication screening and reasons for exclusion is shown in Appendix Fig. 1. We performed our search in PubMed Central in English language. Keywords used were "Impella shock". Databases were screened until 30th of December 2018. The most updated and inclusive data for each study were used for abstraction. References of original and review articles were cross-checked.

Selection criteria and internal validity

Citations were screened on title/abstract level and retrieved as full reports if they fulfilled the inclusion criteria: (1) human studies; (2) studies reporting mortality and outcomes after Impella of more than 10 patients; (3) English language; (4) a control group for Impella consisting of IABP and/or medical treatment. Two independent reviewers (BW and CS) selected the studies, extracted studies and patients' characteristics of interest and relevant outcomes; divergences were resolved by consensus after discussion with a third reviewer (AL).

Study end points

The primary endpoint was short-term mortality (30-day mortality or in-hospital mortality). Secondary endpoints were stroke, major bleeding, and peripheral ischemic complications.

Data synthesis and analysis

Study-level data were analyzed. Heterogeneity was assessed using the I^2 statistic. Risk rates were calculated using a random-effects model (DerSimonian and Laird) for clinical outcomes for each individual study and consecutive pooling [19]. Review Manager 5.3 was used for statistical computations and graphical work-up.

Results

After exclusion of duplicates, 317 studies were screened on title and abstract level. Six studies were identified suitable for a review, and four studies were included in the meta-analysis

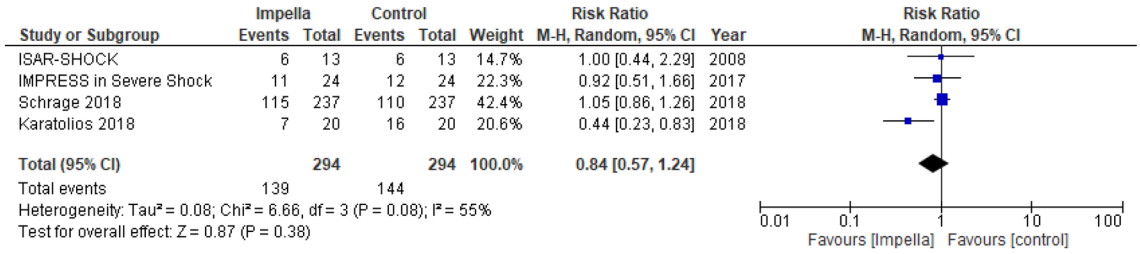

Fig. 1 Forest plot showing risk estimates for short-term mortality

[16, 20–24]. The studies of Manzo-Silberman et al. and Pieri et al. are reviewed collaboratively but excluded from meta-analysis as baseline characteristics between Impella and control were different as explained below [21, 24]. From Karatolios et al., only results from the propensity matched cohort were included in the meta-analysis [23].

Review of studies comparing Impella to control

Baseline characteristics of included studies are shown in Tables 1 and 2.

The ISAR-SHOCK trial was the first randomized study comparing Impella LP2.5 ($n=12$) to IABP ($n=13$) in patients suffering from AMI–CS. In patients supported by Impella, cardiac index was higher, but 1-month mortality did not differ between the two groups [20]. Of note, in this study, Impella was implanted post-PCI in all patients.

Manzo-Silberman conducted a retrospective single-center comparison of Impella LP2.5 ($n=35$) versus IABP ($n=43$) in patients with CA–CS. There were no differences between the two treatments with regards to sequelae-free survival (23% vs 30%; $p=0.61$) and vascular complications. Still, there was a trend towards higher rates of serious bleeding complications in Impella patients. Of note, patients in the Impella group were in significantly more pronounced shock as expressed by higher doses of epinephrine (2.3 mg/h versus 1.0 mg/h; $p=0.04$) and lower LV ejection fraction (25% versus 35%; $p=0.01$).

IMPRESS in severe shock was another randomized, prospective multicenter trial investigating Impella ($n=24$) versus IABP ($n=24$) in patients suffering from AMI–CS. IMPRESS was designed as feasibility trial conducted in patients on mechanical ventilation and high-dose vasopressors. Again, after 1 month, mortality in both groups was equally high (50% vs 46%; $p=0.92$), and after 6 months, mortality was at 50% ($p=0.92$) in both groups. There were three device-related bleeding complications in the Impella group versus one in the IABP group, and in total eight patients suffering from major bleeding in the Impella versus two in the IABP group. Of note, there was numerically better survival (25% vs 53%; $p=0.16$) if Impella or IABP was implanted early (before primary percutaneous coronary intervention).

Karatolios conducted a retrospective, single-center study in patients suffering from CA–CS, comparing Impella ($n=27$) to medical treatment ($n=63$). As patients in the Impella group were sicker indicated by higher lactate levels, longer low-flow duration, and lower LV ejection fraction, the authors matched 20 patients of each group based on a propensity score. In the matched cohort which was well balanced, Impella patients evidenced lower in-hospital (35% vs 80%; $p=0.01$) and 6-month (40% vs 80%; $p=0.02$) mortality. This is the only study reporting a mortality benefit of Impella in the setting of CS. There was one peripheral ischemic complication in the Impella group versus none in the medical treatment arm.

Pieri et al. investigated 64 AMI–CS patients in total, 28 receiving Impella, and 36 patients being treated with IABP [24]. In this study, the patients being treated with Impella suffered from more pronounced shock as indicated by more frequent use of catecholamines (93% vs 57%; $p=0.002$) and higher inotropic scores (8 versus 5; $p=0.02$). Interestingly, though, 30-day mortality was statistically non-dissimilar between Impella and IABP patients (79% vs 94%; $p=0.11$). At 6 months, patients initially treated with Impella evidenced higher LV ejection fraction as well as higher myocardial recovery compared to IABP.

Schrage et al. matched 237 patients from the IABP-SHOCK II trial either receiving IABP ($n=115$) or medical treatment ($n=122$) to 237 Impella patients from a multicenter registry [16]. Patients suffered from AMI–CS, with 85 patients in each group (Impella versus IABP-SHOCK II

Table 1 Main clinical and procedural characteristics (devices and access route) of patients included in this analysis

Study	Year	Patients	Disease	Impella	Control	Setting	Randomization	Follow-up	Included in meta-analysis
ISAR-SHOCK	2008	26	CS due to AMI	2.5	IABP	Multicentre	Yes	30 days	Yes
Manzo-Silberman	2013	78	CS post-cardiac-arrest	2.5	IABP	Single center	No	28 days	No
IMPRESS	2017	48	CS due to AMI	CP	IABP	Multicentre	Yes	30 days	Yes
Karatolios	2018	90	CS post-cardiac-arrest	NA	Medical treatment	Single center	No/matched-control	Hospital discharge/6 months	Yes
Pieri	2018	64	CS due to AMI	2.5 and CP	IABP	Single center	No	6 months	No
Schrage	2018	474	CS due to AMI	2.5 (74); CP (156)	Medical treatment/IABP	Multicentre	No/matched-control	30 days	Yes

AMI acute myocardial infarction, *CS* cardiogenic shock, *IABP* intra-aortic balloon pump

Table 2 Main baseline and post-procedural echocardiographic patient characteristics

Study	ISAR-shock		Manzo-silberman		Impress		Karatolios		Pieri		Schrage	
	Impella	Control	Impella	Control	Impella	Control	Impella	Control	Impella	Control	Impella	Control
n =	13	13	35	43	24	24	20	20	28	36	237	237
Age (years)	65 ± 10	67 ± 19	57(51–70)	62(50–66)	58 ± 9	59 ± 11	65.65 ± 12.81	67.6 ± 11.3	66.3 ± 10.7	65.2 ± 11.7	70(60,78)	71(60,78)
Male gender n (%)	8(62)	11(85)	29(83)	35(81)	18 (75)	20 (83)	17	15	20 (71)	20 (56)	162(68,4)	162(68,4)
CV risk factors												
Arterial hypertension n (%)	7(54)	9(69)	na	na	4 (20)	6 (29)	16 (80)	11 (55)	12 (43)	26 (72)	142(62,0)	168(71,2)
Hyperlipidaemia n(%)	8(62)	7(54)	na	na	4 (20)	5 (24)	na	na	9 (32)	21 (58)	95(43,0)	95(40,4)
Diabetes mellitus n (%)	5(39)	3(23)	na	na	2 (9)	3 (13)	6 (30)	3 (15)	7 (25)	11 (31)	78(34,1)	86(36,3)
Current smoking n (%)	8(62)	7(54)	na	na	11 (61)	6 (32)	na	na	3 (11)	18 (50)	52(27,4)	78(33,1)
Baseline characteristics												
Multi vessel CAD n (%)	9(69)	10(77)	23	29	15 (63)	21 (88)	14(70)	15(75)	19 (68)	10 (56)	173(75,2)	185(78,7)
TIMI flow 2 or 3 post-PCI n (%)	12(92)	12(92)	na	na	23 (96)	24 (100)	na	na	na	na	na	na
Device implantation pre-PCI n (%)	0	0	na	na	5 (21)	3 (13)	6	na	12 (43)	21 (58)	na	na
AMI n (%)	13(100)	13(100)	na	na	24 (100)	24 (100)	na	na	28 (100)	36 (100)	na	na
Anterior AMI n (%)	7(54)	8(62)	na	na	16 (67)	15 (63)	na	na	20 (71)	23 (64)	na	na
Catecholamines n (%)	11(85)	12(92)	31(89)	33(76)	24 (100)	24 (100)	20(100)	20(100)	26 (93)	20 (57)	181(77,0)	166(76,5)
Mechanical ventilation n (%)	12(92)	12(92)	na	na	24 (100)	24 (100)	20(100)	20(100)	17 (61)	18 (50)	131(55,3)	131(55,3)
CPR n (%)	11(85)	9(69)	na	na	24 (100)	20 (83)	20(100)	20(100)	0 (0)	0 (0)	85(35,9)	85(35,9)
LV-EF (%)	28 ± 14	31 ± 16	25(20–35)	35(25–40)	30 ± 16	28 ± 16	na	na	21 ± 7	26 ± 8	25(20,35)	25(20,35)

CV cardiovascular, *CAD* coronary artery disease, *AMI* acute myocardial infarction, *CPR* cardiopulmonary reanimation, *LV-EF* left-ventricular ejection fraction

group) with prior cardiopulmonary reanimation (CPR). There was no difference in 30-day mortality (49% vs 46%; $p=0.64$) but higher rates of major bleeding (9% vs 3%; $p<0.01$) and peripheral ischemic complications (10% vs 4%; $p=0.01$) in the Impella group. Again, in none of the investigated subgroups (patients with and without prior CPR, Impella implantation before versus after PCI, Impella CP and Impella LP2.5), Impella was associated with increased survival.

Meta-analysis of studies comparing Impella to control

In a meta-analysis of four studies comparing Impella versus control, Impella was not associated with improved short-term mortality (in-hospital or 30-day mortality; RR 0.84; 95% CI 0.57–1.24; $p=0.38$; I^2 55%; Fig. 1). Stroke risk was not increased (RR 1.00; 95% CI 0.36–2.81; $p=1.00$; I^2 0%; Fig. 2), but risk for major bleeding (RR 3.11 95% CI 1.50–6.44; $p=0.002$; I^2 0%; Fig. 3) and peripheral ischemia complications (RR 2.58; 95% CI 1.24–5.34; $p=0.01$; I^2 0%; Fig. 4) were increased in the Impella group.

Discussion

In this meta-analysis of all available trials comparing Impella versus control (medical treatment or IABP), Impella was not associated with 30-day survival in patients with AMI–CS or CA–CS, but the use of Impella was associated with higher rates of bleeding and peripheral ischemic complications.

Impella was shown to increase cardiac output and mean arterial blood pressure improving end-organ perfusion both in patients suffering from CS and pre-CS [20]. In a sheep model of AMI, Impella was shown to reduce oxygen consumption leading to a reduction in infract size [25]. In another animal model, Impella unloaded the left ventricle and improved tissue perfusion [26]. As Impella is thought to help unloading the left ventricle, it was successfully combined with veno-arterial extra corporal life support (VA-ECLS) to wean patients from VA-ECLS [27]. Therefore, Impella could play a role in augmenting VA-ECLS in the future [28]. A small registry compared patients suffering from refractory CS on VA-ECLS—another, highly invasive therapy for CS usually needing surgical backup—to Impella: In this study, Impella was non-inferior after adjustment for

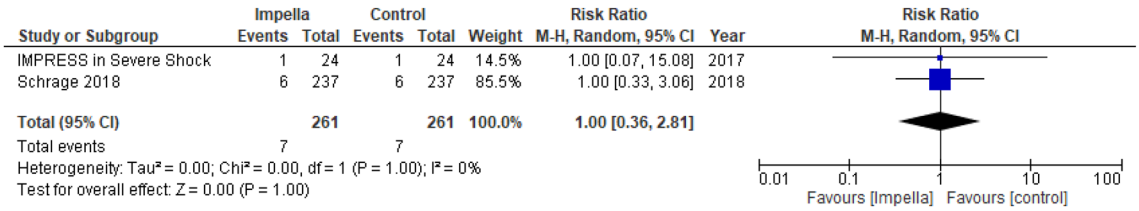

Fig. 2 Forest plot showing risk estimates for short-term stroke rate

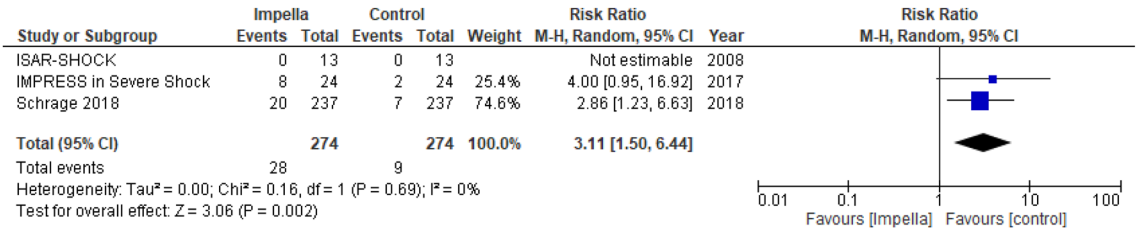

Fig. 3 Forest plot showing risk estimates for short-term major bleeding

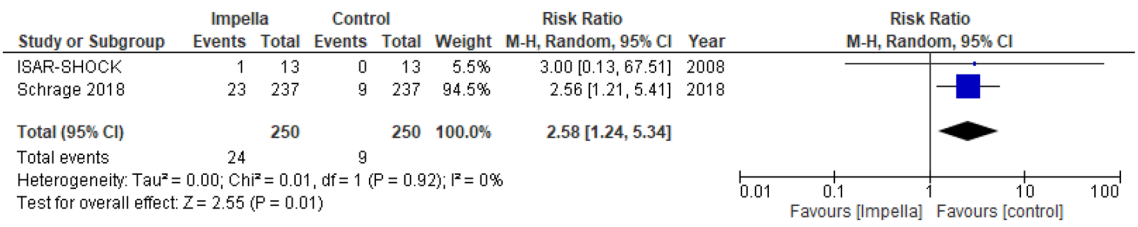

Fig. 4 Forest plot showing risk estimates for peripheral ischemic complications

disease severity [29]. In the Impella-EUROSHOCK registry, a retrospective study investigating 120 CS patients Impella LP2.5 evidenced feasible usage and reduced lactate levels [8]. In a rural community hospital without heart surgical backup, Impella was evaluated in patients suffering from AMI–CS: In this study, Impella was associated with survival rates around 60% and a recovery of LV function in 89% [30]. Recently, a large series ($n = 250$) of patients treated with Impella for CS reported feasibility with vascular complications at 17% and stroke at 3.6%, and a 30-day mortality of 56% from 2004 to 2016 [31]. Besides CS, Impella was successfully employed in high-risk PCI, myocarditis, and ventricular tachycardia ablation [32–35].

Still, to date, only one retrospective study of CA–CS patients reported increased survival in Impella patients compared to best medical treatment [23]. In this meta-analysis, no difference with regards to short-term mortality could be found comparing Impella to control, which is in accordance to the previous studies comparing fewer patients [36]. Patients included in the cohorts investigated in this study suffered from profound CS, with high rates of catecholamine use including many patients with prior cardiac arrest, implying high likelihood of neurological damage due to transient hypoxia. In these patients, an increase in cardiac output attained by Impella might be futile as the (neurological, cardiac, and peripheral) damage done by hypoperfusion and hypoxia is already irreversible. Approaches to reliably identify these patients of immutable fate would be of tremendous help to avoid "useless" treatment, but are extremely difficult to develop.

Compared to IABP insertion via a 7–8 French sheath or even sheath-less insertion, Impella LP2-5 and CP are inserted via 12 and 13 French sheaths, which might contribute to increased risk of peripheral ischemic complication and bleeding in the Impella group. These increased rates of bleeding and vascular complications might further contribute to higher rates of sepsis in the Impella group observed in the study of Schrage et al. Hemodynamic improvements of the Impella might be annihilated by these higher complication rates. Limiting these complications via, e.g., smaller delivery systems could help to improve outcomes using the Impella in CS patients.

Many patients investigated here were treated with Impella LP2.5 which can achieve up to 2.5 l/min of additional forward flow—this still might be too little to avoid or ease systemic inflammatory response syndrome in severe CS, especially if peripheral vasoconstriction further impairs end-organ perfusion. Even Impella CP reaches 3.5 l/min cardiac output only at its best, and in daily practice, lower flow rates are observed. Therefore, more potent pMCS devices such as Impella 5.0 might help to improve outcomes providing higher flow rates leading to a better peripheral perfusion. Still, in daily practice, the use of Impella 5.0 is limited as in contrast to Impella LP2.5 and CP Impella 5.0 warrants surgical intervention which is usually slower.

With regards to timing, in IMPRESS in Severe Shock, early pMCS insertion was associated with numerically lower mortality. Data from the USpella registry indicated an independent favorable association of early Impella implantation with outcome even after correction for confounders [37]. In a recent retrospective single-center study of AMI–CS and CA–CS patients, Impella CP implantation prior to PCI was associated with decreased hospital mortality [38]. Recently, in a safety study, Kapur et al. could show that, in STEMI patients, early Impella CP implantation is feasible [39]. In another study, survival rates were higher in patients with door-to-Impella time ≤ 48 min [30]. Similar findings were summarized in a meta-analysis indicating a role for early Impella implantation in a total of 379 patients [40]. Still, in the recent large study of Schrage et al., this finding could not be confirmed [16]: this could be interpreted as signal that patients in this particular study were already beyond a "point-of-no-return", where timing of implantation does simply not matter—anymore. On the other hand, in the study of Schrage et al., early Impella implantation was defined as pre-PCI implantation—therefore, these results need to be interpreted cautiously. Future studies evaluating effects of early versus late pMCS implantation are warranted. To improve outcomes in patients suffering from CS, protocols including clinical assessment and biomarkers to enable earlier Impella implantation could be developed [41–45]. Certainly, the results of the DanGer Shock trial (NCT01633502) are eagerly awaited, a trial started in Denmark and recently being expanded to Germany planning to include a total of 360 patients. Included patients suffer from acute STEMI (< 36 h), AMI–CS for < 24 h. AMI–CS will be confirmed by lactate concentration ≥ 2.5 mmol/L, blood pressure < 100 mmHg, and/or vasopressor therapy at an LV ejection fraction below 45%. Patients treated with Impella CP compared to standard care will be assessed at a primary outcome of 6-month mortality. This study will most likely add a significant insight on the potential value of Impella in CS patients.

Limitations

Although combining all available data comparing Impella versus control, total patient numbers remain low. Due to the low total study number, we used random-effect models even in the presence of low formal heterogeneity. The inclusion of two non-randomized observational retrospective studies in this meta-analysis is a limitation of our findings. Due to the lack of individual patient data, an evaluation of potential sub-groups benefiting from Impella was impossible, and furthermore, no comparison of distinct Impella devices and other sub-groups could be made. Still, this study comparing Impella versus control reports data on mortality on the largest cohort available to date.

Conclusion

Based on the currently available registry data, the use of the Impella does not improve survival in patients suffering from severe CS due to AMI–CS and CA–CS. However, compared to IABP and medical treatment, use of the Impella comes at higher rates of bleeding and ischemic complications. As data from randomized trials supporting the use of the Impella in individual patient populations are lacking, the indication for this treatment should be made critically and balanced with the risk of device-associated adverse events. The concept of percutaneous support is intriguing; however, outcome-driven randomized studies are needed to identify sub-groups of patients with potential benefit from this treatment.

Funding No (industry) sponsorship has been received for this study.

Data availability All data relevant for this study will be given by the authors upon specific request without restriction.

Compliance with ethical standards

Conflict of interest The authors report no relationships that could be construed as a conflict of interest.

Appendix

See Appendix Fig. 5.

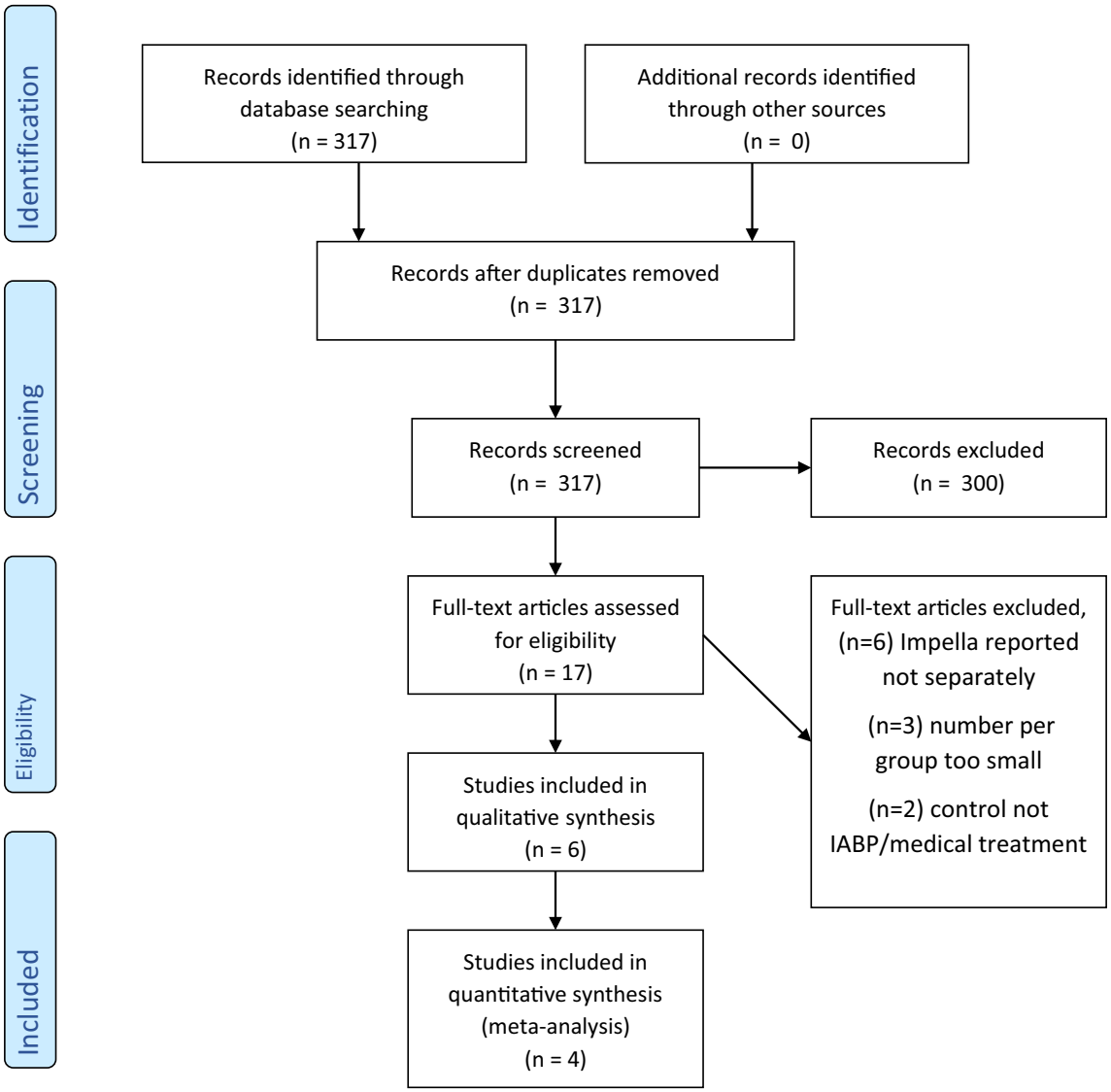

Fig. 5 PRISMA flowchart illustrating publication screening

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