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REVIEW ARTICLE

Steroid withdrawal after heart transplantation in adults

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SUMMARY

Corticosteroids (CSs) are a key component of immunosuppressive treatment after heart transplantation (HTx). While effectively preventing acute rejection, several adverse effects including diabetes, hypertension, osteoporosis, and hyperlipidemia are associated with long-term use. As these complications may impair long-term outcome in HTx recipients, withdrawal of CSs is highly desirable, however, no uniform approach exists. Previous experience suggests that CS withdrawal can be accomplished without an increase in the incidence of acute rejection and even carrying a survival benefit. Also, common complications related to long-term CS use appear to be less frequent following CS discontinuation. Recipients who successfully discontinue CSs, however, likely belong to an immune-privileged subset of patients with low risk of post-transplant complications. Available studies evaluating CS withdrawal are highly heterogeneous and consensus on optimal timing and eligibility for withdrawal is lacking. Efforts to improve the understanding of optimal CS withdrawal strategy are of great importance in order to safely promote CS weaning in eligible patients and thereby alleviate the adverse effects of long-term CS use on post-transplant outcomes. The purpose of this review was to evaluate different protocols of CS withdrawal after HTx in terms of clinical outcomes and to explore criteria for successful CS withdrawal.

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Key words
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Introduction

Heart transplantation (HTx) is the definitive treatment option in selected patients with end-stage heart failure. Post-transplant outcomes have improved significantly over time with a median survival exceeding 12 years [1]. Life-long immunosuppressive therapy is essential post-transplant to suppress the mechanisms of allograft rejection and thereby preserve graft function and survival [2]. Maintenance immunosuppressive drugs act on different specific lymphocyte targets and are traditionally administered in triple-drug regimens consisting of a calcineurin inhibitor (CNI), an antimetabolite, and a corticosteroid (CS) [3]. Components of this regimen can be substituted or rarely supplemented with a mammalian target of rapamycin (mTOR) inhibitor [4]. Besides being a cornerstone of most maintenance protocols, CSs play an important role in the treatment of acute rejection episodes [1,5]. According to data from the International Society for Heart and Lung Transplantation (ISHLT) Registry, 80% of HTx recipients receive CS treatment at 1-year post-transplant [1].

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Although the immunosuppressive effects of CSs are highly beneficial in terms of prevention and treatment of acute rejection, especially early post-transplant, multiple adverse effects associated with long-term use of CSs might compromise successful outcome in HTx recipients [6]. Efforts to minimize CS exposure post-HTx are expected to alleviate the impact of these complications on post-transplant outcomes; however, there is no consensus on optimal CS withdrawal protocol, and both timing and eligibility for successful withdrawal remain unclear [5]. The purpose of this review was to evaluate different protocols of CS withdrawal after HTx in relation to clinical outcomes.

Methods

A systematic literature search in PubMed up to April 2020 was conducted to identify studies evaluating CS withdrawal after HTx. The string of key words inputted in PubMed was "heart transplantation OR cardiac transplantation AND transplantation AND steroid OR glucocorticoid OR prednisone AND withdrawal AND taper AND weaning OR heart transplantation steroid withdrawal OR heart transplantation steroid weaning." Articles written in English and published between January 1992 and April 2020 were included. Studies evaluating pediatric HTx and multiorgan transplantation were excluded as were studies evaluating CS avoidance or CS minimization protocols. In total, 26 studies were identified and grouped according to protocol for CS withdrawal. The selection process is illustrated in Fig. 1. Steroid withdrawal protocols were classified according to timing of withdrawal into *early* (within the first 6 months post-HTx), *late* (beyond 6 months post-HTx), and *not reported* (unspecified timing of withdrawal). We evaluated maintenance immunosuppression, withdrawal efficacy, survival, acute rejection, and long-term complications to CS treatment. Recipients withdrawn from CS and recipients maintained on CS are termed *CSw* and *CSm*, respectively, throughout this review.

Corticosteroids

Mechanisms of action

Corticosteroids offer potent immunosuppressive and anti-inflammatory properties and thereby suppress the immunologic mechanisms leading to acute rejection [7]. They exert their actions by binding to intracellular glucocorticoid receptors. The receptor-steroid complex translocates to the nucleus, where it regulates transcription of target genes. This results in altered expression of genes involved in the immune and inflammatory response [3]. Corticosteroids affect the function of leukocytes (T and B lymphocytes, granulocytes, macrophages, and monocytes) and endothelial cells. The effects on leukocytes are mainly mediated by the inhibition of two transcription factors, activator protein-1 and nuclear factor kappa B (NF-kappa B) [8,9]. In non-lymphoid cells, CSs cause a decrease in the production of vasoactive and chemoattractant factors as well as proteolytic and lipolytic enzymes, which results in inhibition of neutrophil adhesion to endothelial cells, downregulation of endothelial function, and prevention of macrophage differentiation [3].

Adverse effects

Treatment with CSs carries risk of a number of adverse effects, which are most pronounced with long-term administration. Table 1 summarizes the long-term adverse effects, which include hypertension, diabetes, obesity, dyslipidemia, and osteoporosis [6]. A population-based study from 2006 demonstrated that up to 90% of patients treated with CSs for more than 60 days experienced at least one adverse effect [10]. The adverse effects with greatest self-reported prevalence were weight gain, skin bruising/thinning, and sleep disturbances. Another nontransplant study reported that patients receiving more than the equivalent of 7.5 mg prednisolone/day during 1–5 years of follow-up had a significantly higher risk for cardiovascular events when compared with CS nonusers [11]. Patients with high-dose CS exposure were found to have a significantly increased risk for myocardial infarction, cerebrovascular events, and all-cause mortality. The association between CS exposure and cardiovascular disease might in part be explained by the exacerbation of conventional cardiovascular risk factors caused by CS use [6,11]. Together, the burden of adverse effects emphasizes the importance of exploring the possibility to minimize CS exposure post-HTx.

Corticosteroid withdrawal

The use of CS agents in maintenance HTx protocols has changed notably over the past 20 years with a trend toward minimization of CS exposure. According to the ISHLT Registry, approximately 6% of patients were withdrawn from CS at 1 year post-HTx in 2000 [12] compared with 20% of patients in 2018 [1].

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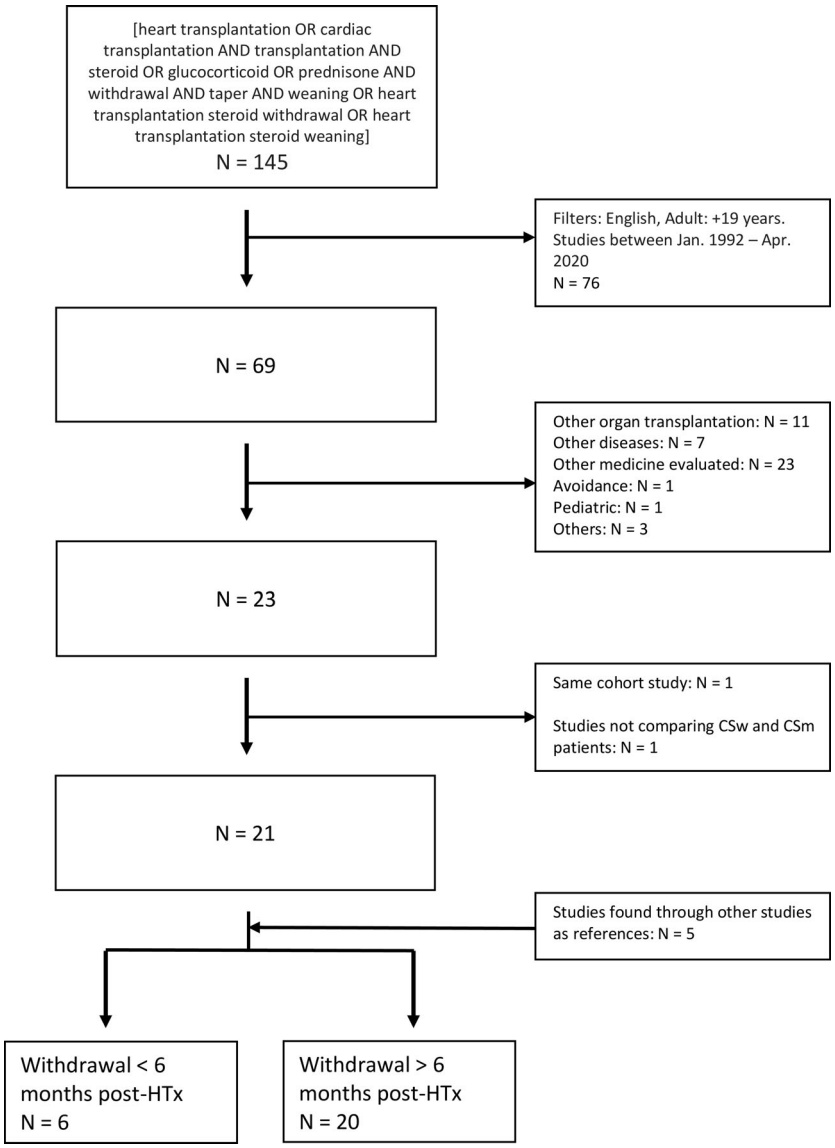

Figure 1 Flowchart of the selection of studies investigating withdrawal of corticosteroid after heart transplantation.

Reducing CS exposure after HTx strikes a balance between avoiding the long-term adverse effects associated with chronic CS use, without causing excess acute rejection which might compromise allograft function. The ISHLT recommendations state that weaning of CS should be attempted in case of significant CS side effects or in the absence of recent rejection episodes [5]. Endomyocardial biopsy is considered the standard of care for surveillance of acute allograft rejection, both before and after CS withdrawal. Among currently accepted strategies enabling reduction of CS exposure are CS avoidance, CS withdrawal (*early* or *late* post-HTx), and CS minimization in maintenance protocols [5]. No universally accepted withdrawal protocol exists and optimal timing of CS withdrawal after HTx remains unsettled. Consequently, a variety of different withdrawal protocols have been used, and no consensus on selection criteria for weaning exists. Protocols completely devoid of steroids have been reported [13] but are beyond the scope of this review.

Withdrawal before 6 months post-HTx

Corticosteroid withdrawal before 6 months post-HTx has been systematically investigated in six different studies from 1992 to 2018. *Early* withdrawal studies are summarized in Table 2.

In four retrospective studies with cyclosporine-based maintenance regimen, the proportion of patients experiencing successful withdrawal ranged from 30% [14] to 81% [15]. Pritzker *et al.* [15] suggested that the use of OKT3 induction therapy allowed a high success rate for

Table 1. Long-term adverse effects of corticosteroid treatment.

System affected	Adverse effect	Proposed mechanism
Musculoskeletal	Osteoporosis	Inhibition of osteoblast function → decrease in bone formation [6]
	Osteonecrosis	Induction of osteocyte apoptosis → affecting bone remodelling [6]
	Myopathy	Decrease in protein synthesis and increase in protein catabolism → muscle atrophy [6]
Endocrine and metabolic	Hyperglycemia, diabetes mellitus	Impaired glucose metabolism [59,60]
	Dyslipidemia	Induction of lipolysis, increase in synthesis of VLDL, production of free fatty acids and their accumulation in the liver [6]
	Cushingoid features, weight gain	Redistribution of body fat and increased appetite [6]
	Adrenal suppression	Exogenous glucocorticoid administration can suppress the HPA axis (challenges tapering or withdrawal) [6]
Cardiovascular	Hypertension	Presumably mediated by vasoactive substances and as a result of weight gain [6]
	Ischemic heart disease, heart failure	Secondary to hypertension, hyperglycemia, and dyslipidemia [6]
Gastrointestinal	Gastritis, peptic ulcer formation, gastrointestinal bleeding	–
	Hepatic steatosis, pancreatitis, visceral perforation	–
Dermatologic	Poor wound healing	Catabolic effects of CSs [6]
	Bruising, acne, hirsutism, skin fragility	–
Neuropsychiatric	Mood changes, depression, euphoria, emotional lability, anxiety, cognitive impairment	–
Ophthalmologic	Cataract, glaucoma	Change in gene transcription in lens epithelial cells, alterations in levels of intraocular growth factors, increased intraocular pressure [6]
Immunologic	Predisposition to infection, reactivation of latent infection	Immunosuppressive effects of CSs [6]

CS, corticosteroid; HPA, hypothalamic-pituitary-adrenal; VLDL, very low-density lipoprotein.
Modified from Oray *et al.* [6].

CS withdrawal. In the largest study from 1996, Taylor *et al.* [14] concluded that successful early CS withdrawal identified a subgroup of immune-privileged patients. Withdrawal was attempted within 2 months of HTx and was possible in 30% of eligible patients. Later, Rosenbaum *et al.* [16] found that 57% of patients eligible for steroid taper were successfully withdrawn at 6 months post-HTx. Where specified, successful weaning was defined by the absence of each of the following: recurrent episodes of acute rejection, any rejection with hemodynamic compromise, acute vascular rejection, leukopenia, renal insufficiency, or any other indication for CS treatment [16,17].

Two prospective studies also reported differing withdrawal efficacy. Olivari *et al.* [18] found that 42% of patients receiving standard triple-therapy were successfully withdrawn from CS by 6 months post-HTx. More recently, Baran *et al.* [19] investigated CS weaning in stable HTx recipients by the guidance of morning cortisol. Patients were at least 4 months post-HTx and received tacrolimus-based maintenance therapy. Of patients assigned to steroid weaning, none resumed CS treatment following discontinuation and no episodes of grade ≥2R rejection or unexplained graft dysfunction occurred within a mean follow-up of approximately 10 years.

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Table 2. Studies investigating corticosteroid withdrawal before 6 months post-HTx.

Author (year)	Design	*N*	Maintenance regimen	CS withdrawn successfully (%)	Biopsy protocol following CS withdrawal	Definition of successful withdrawal	Follow-up time after CS withdrawal	CS-related complications evaluated	Rejection	Survival
Pritzker (1992) [15]	Retrospective	68	CyA + AZA + CS (+OKT3 for CSw)	81	–	–	12 months	Infection Hypertension Dyslipidemia	NS	Significantly better in CSw
Lake (1993) [17]	Retrospective	89	CyA + AZA + CS	78	–	–	24 months	Dyslipidemia Obesity	–	–
Olivari (1995) [18]	Prospective	84	CyA + AZA + CS	42	Every 2 weeks until patients had not received CS for at least 2 months → hereafter monthly until 1 year after withdrawal → every 3 months	No more than one episode of acute graft rejection	3.5–5.5 years	Dyslipidemia Weight Hypertension Infection Bone loss CAV	Significantly higher in CSw	NS
Taylor (1996) [14]	Retrospective	374	CyA + AZA + CS	30		–	–	CAV	Significantly lower in CSw	Significantly better in CSw
Rosenbaum (2006) [16]	Retrospective	139	CyA + AZA + CS	57		No more than two episodes of rejection, hemodynamic compromise, leukopenia, acute vascular rejection or renal insufficiency	Mean 10.0–10.8 years	Infection Malignancy CAV	Significantly higher in CSw	NS
Baran (2018) [19]	Prospective	31	TAC + MMF + CS	100	At least 1 biopsy within the first 2 months after withdrawal	No rejection ≥grade 2R or AMR	10 years	–	No episodes ≥2R in CSw	NS

This table presents an overview of studies investigating CS withdrawal before 6 months post-HTx in adult recipients. Only studies written in English and published between January 1992 and April 2020 are included (n = 6).

2R, moderate rejection according to the ISHLT 2004 criteria; AMR, antibody-mediated rejection; AZA, azathioprine; CAV, cardiac allograft vasculopathy; CS, corticosteroid; CSm, corticosteroid maintenance group; CSw, corticosteroid withdrawal group; CyA, cyclosporine; MMF, mycophenolate mofetil; TAC, tacrolimus.

The follow-up time after CS withdrawal differed substantially among studies, ranging from 12 months in a retrospective study [15] to approximately 10 years in both a retrospective and prospective study [16,19]. The International Society for Heart and Lung Transplantation reports a median survival after HTx of 12 years [1], suggesting that longer follow-up time would be advantageous when investigating the long-term effects of CS administration.

Withdrawal after 6 months post-HTx

Corticosteroid withdrawal beyond 6 months post-HTx has been investigated in 20 studies from 1992 to 2017. Withdrawal approach varied considerably, and definition of successful CS withdrawal was not uniform among studies. Follow-up time also differed in these studies, ranging from 6 months [20,21] to 13 years [22]. *Late* withdrawal studies are summarized in Table 3.

The retrospective studies demonstrated success rates of CS withdrawal ranging from 22% [23] to 92% [24]. In the largest cohort of 1209 HTx recipients, Crespo-Leiro *et al.* [23] found a 5-year post-HTx incidence of successful CS withdrawal of only 22%. Twenty-one percent of patients weaned from CS at some point required reintroduction of CS within 5 years post-HTx. The relatively low success rate of CS withdrawal was explained by an over-conservative approach with regard to CS reintroduction. The highest reported success rate of 92% was achieved in patients selected for a CS weaning protocol initiated from 6 months post-HTx [24]. Generally, stable patients without recent moderate-severe rejection were considered eligible for CS withdrawal and uneventful withdrawal without the occurrence of rejection was classified as successful [20–22,25–28]. Several studies did, however, not specifically report selection criteria for CS withdrawal or definition of successful CS withdrawal [23,24,29,30].

In the prospective studies, rate of successful CS withdrawal ranged from 44% [31] to 82% [32,33]. Reported success rate might to some extent reflect the follow-up time after CS weaning and classification of CS reintroduction in terms of failed withdrawal. In a largest cohort, evaluating CS withdrawal in low-risk patients at a median of 1.4 years post-HTx, the cumulative rate of patients requiring steroids at any time was 55.7% at 5 years after CS withdrawal [31]. Eligibility for CS withdrawal generally entailed stable graft function and renal function as well as absence of immunologic high-risk conditions [31,34–36]. Patients were widely considered successfully weaned if no acute rejection episodes occurred; however, this was not uniformly defined [32,34,35,37–39].

Considerations in corticosteroid withdrawal

Acute allograft rejection

Acute rejection is among the leading causes of death post-HTx [1] and is therefore an important concern in post-transplant care and a main focus of CS withdrawal protocols. Whether or not CS withdrawal leads to an increased incidence of acute rejection remains controversial. A main limitation to observational studies in this area is that steroid weaning in most cases causes physicians to perform an extra endomyocardial biopsy in addition to protocol-based biopsies. This carries the risk of detecting a self-limiting rejection infiltrate which would otherwise have remained undetected.

Early CS withdrawal studies report conflicting results. A recent prospective study demonstrated no rejection ≥2R in CSw patients [19], whereas a previous retrospective study found significantly lower prevalence of late acute rejection (>1 year post-HTx) in patients successfully weaned from CS [14]. Two studies reported a significantly higher incidence of acute rejection in CSw compared with CSm patients [16,18]. Perhaps contributory, a more comprehensive endomyocardial biopsy surveillance protocol was applied in CSw patients [16]. Of note, recurrent rejection might also render withdrawal attempt unsuccessful.

Several prospective *late* withdrawal studies demonstrated no significant difference in the incidence of acute rejection between CSw and CSm patients [31,32,38,40]. Similar results were found in two retrospective studies [21,26], whereas four retrospective studies found less rejection episodes in CSw patients [25,28,29,35]. None of the *late* withdrawal studies reported higher incidence of rejection in CSw patients.

Importantly, patients experiencing recurrent and more severe rejection are more likely maintained on CS treatment in observational studies, which could be a reasonable explanation for the results presented above. Also, patients who tolerate CS withdrawal might have a more benign risk profile in terms of rejection and thus experience less rejection even following withdrawal. Conclusions regarding the association between CS weaning and incidence of acute rejection should therefore be drawn cautiously, as selection of patients for withdrawal might constitute an important bias. It does, however, appear that withdrawal beyond 6 months post-HTx can be safely accomplished. Antibody-mediated rejection (AMR) and donor-specific antibodies (DSA) are also relevant concerns in CS withdrawal. In 2017, Elboudwarej *et al.* [28] demonstrated a higher

Table 3. Studies investigating corticosteroid withdrawal after 6 months post-HTx.

Author (year)	Design	*N*	Maintenance regimen	CS withdrawn successfully (%)	Biopsy protocol following CS withdrawal	Successful withdrawal definition	Follow-up time	CS-related complications evaluated	Rejection	Survival
Miller (1992) [32]	Prospective	48	CyA + AZA + CS	82%	First at initiation of withdrawal → at dose 2.5 mg/day → at completion of withdrawal → hereafter monthly for 4 months → every 3 months	No more than one rejection episode after withdrawal	Mean 25 months	Hypertension Dyslipidemia Weight	NS	–
Kobashiqawa (1992) [38]	Prospective	68	CyA + AZA + CS	80%	Monthly up to 2 months after withdrawal	–	–	–	NS	–
Kobashiqawa (1995) [33]	Prospective	101	Triple-drug	82%	Monthly during withdrawal period + 2 months after withdrawal	No episodes of moderate rejection		Weight Dyslipidemia	–	–
Seydoux (1997) [21]	Retrospective	64	CyA + AZA + CS	–	–	–	>6 months	Infection	NS	–
Delgado (1999) [40]	Prospective	44	CyA + AZA + CS	–	–	–	CSw: Median: 47 months CSm: Median 69.9 months	Infection Hypertension	NS	–
Oaks (2001) [20]	Retrospective	56	CyA + AZA + CS/ CyA + MMF + CS	1 year: 12% 2 years: 75%	1 and 2 months after withdrawal or in case of clinical symptoms	No biopsies >grade 2A	6 months – 2 years	–	–	–
Baran (2001) [36]	Prospective	77	CyA based triple-drug/ TAC + CS/TAC		–	No rejection ≥grade 2 or hemodynamic instability	726 ± 366 days	–	–	Significantly better in CSw
Felkel (2002) [25]	Retrospective	137	CyA + AZA + CS	52.5%	–	–	2–8 years (+5 years for survival)	Weight Renal function	Significantly l ower in CSw	Significantly better in CSw
Baran (2002) [37]	Prospective	68	TAC + CS	75%	–	No rejection >grade 2A	Mean 2.3 ± 1.4 years	PTDM	–	–
Uber (2002) [39]	Prospective	104	TAC/ CyA + MMF + CS	–	–	No clinically significant rejection	1.3 ± 2 years	BNP	–	–
Mehra (2004) [35]	Prospective	41	TAC + MMF + CS	62%	–	–	47 ± 5 months	Infection Hypertension Hyperglycemia	Significantly lower in CSw	–

Table 3. Continued.

Author (year)	Design	*N*	Maintenance regimen	CS withdrawn successfully (%)	Biopsy protocol following CS withdrawal	Successful withdrawal definition	Follow-up time	CS-related complications evaluated	Rejection	Survival
Opelz (2005) [31]	Prospective	1680	CyA based	5 years: 44.3%	–	No deterioration of cardiac function and no more than two attempts at withdrawal	Median 6.3 years	–	NS	NS
Yong (2007) [22]	Retrospective	56	TAC/ CyA + MMF + CS or CyA + AZA + CS	64%	2 weeks after withdrawal		5–13 years	Osteoporosis	–	NS
Teuteberg (2008) [26]	Retrospective	165	CyA + AZA + CS/ TAC + MMF + CS	1 year: 82%	–	No rejection episodes and clinical stability	1–6 years	PTDM	NS	NS
Castel (2009) [34]	Prospective	86	CyA/TAC + MMF/ AZA + CS	63%	At 1 and 3 months after withdrawal	No rejection ≥grade 2 for 2 successive biopsies	Mean 25 ± 13 months	Dyslipidemia	–	–
Lizak (2011) [29]	Retrospective	76	CyA + AZA/ MMF + CS		–	–	5 years	Infection CAV Dyslipidemia PTDM	Significantly lower in CSw	NS
Nawaz (2011) [27]	Retrospective	174	CyA + MMF + CS		–	–	–	–	–	–
Crespo-Leiro (2012) [23]	Retrospective	1209	–	1 year: 9.9% 5 years: 22%	–	–	5 years	Hypertension PTDM Osteoporosis	–	–
Kittleson (2013) [24]	Retrospective	577	–	92%		No rejection or side effects of withdrawal	5 years	CAV MACE	–	Significantly better in CSw
Elboudwarej (2017) [28]	Retrospective	178	CyA/ TAC + MMF + CS	81%	Every month	No rejection and tolerable side effects of withdrawal	–	–	Significantly lower in CSw	–

AZA, azathioprine; BNP, B-type natriuretic peptide; CAV, cardiac allograft vasculopathy; CS, corticosteroid; CSm, corticosteroid maintenance group; CSw, corticosteroid withdrawal group; CyA, cyclosporine; LDL, low-density lipoprotein; MACE, major adverse cardiac events; MMF, mycophenolate mofetil; PTDM, post-transplant diabetes mellitus; TAC, tacrolimus.

This table presents an overview of studies investigating CS withdrawal beyond 6 months post-HTx in adult recipients. Only studies written in English and published between January 1992 and April 2020 are included (n = 20).

incidence of DSA in CSm patients, which could relate to pretransplant immunologic risk profile. To our knowledge, no dedicated studies have addressed the role of DSA and AMR in CS weaning protocols, but this will hopefully be further explored in future studies.

Survival

In a retrospective study from 2011, Nawaz *et al.* [27] suggested that long-term CS treatment after HTx might be a poor prognostic factor, as 69% of deceased patients were still treated with CSs at the time of death. Similarly, Jiménez *et al.* [30] found that patients who were unable to discontinue CS had a numerically higher mortality rate at 4 years post-HTx.

Five studies with *early* CS withdrawal have investigated survival of HTx patients and demonstrated similar [16,18,19] or superior [14,15] survival in CSw patients compared with CSm patients. As for studies investigating *late* CS withdrawal, one prospective [31] and four retrospective [22,26,29,30] studies found no difference in survival, while three studies demonstrated superior survival in CSw patients [24,25,36]. Overall, survival of CSw patients appeared to be similar or superior to the survival of CSm patients regardless of timing of withdrawal. This might reflect the adverse contribution of CS-related complications to long-term prognosis; however, it might also reflect that high-risk patients, more prone to experience poor long-term outcome, were also less likely withdrawn from CS treatment.

Cardiac allograft vasculopathy

Cardiac allograft vasculopathy (CAV) remains an important limitation to long-term survival after HTx and has a reported incidence of almost 50% at 10 years post-HTx [1]. Etiology is not fully understood but is believed to be multifactorial with both immunologic and nonimmunologic contributions. Level of CS use might influence risk factors in CAV development and possibly with oppositely directed effects. The metabolic complications to long-term CS administration, including hypertension, dyslipidemia, obesity, and diabetes mellitus are known risk factors for CAV [41]. In support of this, Caforio *et al.* [42] reported that higher CS dose at 1 year post-HTx was a risk factor for CAV development, and Price *et al.* [43] demonstrated an association between cumulative CS dose and risk of CAV development. This suggests that CS withdrawal might be beneficial in terms of alleviating CAV. Kittleson *et al.* [24] did, however, not find 5-year freedom from CAV to be significantly higher in (*late*) CSw compared with CSm patients.

Another aspect, however, is the association between acute rejection and CAV [42,44,45] suggesting that an increase in the incidence of acute rejection following CS withdrawal might fuel the immunologic contribution to CAV pathogenesis [46,47]. In 2004, Caforio *et al.* [42] found that high rejection score was associated with increased risk of CAV development, and subsequent studies supported an association between moderate-severe rejection and CAV [44,45]. Peled *et al.* [48] reported that recurrent mild rejection was associated with a higher risk of CAV-related mortality, however, a substudy of the SCHEDULE trial did not find an association between the burden of mild rejection and development of CAV [49].

Reports on CAV as an endpoint in CS withdrawal protocols are sparse. Rosenbaum *et al.* [16] reported that despite greater freedom from acute rejection in CSm patients compared with CSw patients, freedom from CAV was not significantly altered by *early* CS withdrawal. This is consistent with previous findings [14,18,43].

Infection

Due to the immunosuppressive actions of CS, a decrease in the burden of infection is a desired result of withdrawal protocols. The association between CS withdrawal and infection after HTx, however, is not well described. Both studies with *late* [21,29,40] and *early* CS withdrawal [16] have suggested that rate of infection in CSw patients was either similar to that of CSm patients or slightly decreased, although differences were not statistically significant. Two prospective studies demonstrated significantly lower infection rate in CSw patients compared with CSm patients, in both an *early* [18] and a *late* [35] withdrawal setting.

Hypertension

The incidence of hypertension following CS withdrawal has been sparsely investigated. Three prospective studies with *late* withdrawal found no significant difference in the incidence of hypertension between CSm and CSw patients [32,35,40]. However, the incidence of hypertension has also been reported to be significantly lower in CSw patients [23,43].

Diabetes mellitus

A retrospective study with *late* CS withdrawal, found the incidence of post-transplant diabetes mellitus

(PTDM) to be higher in CSw patients compared with CSm patients at 5 years after HTx [29]. Several studies have, however, demonstrated no significant difference in terms of PTDM and hyperglycemia between CSw and CSm patients [13,23,26,35], likely reflecting that diabetes risk after HTx is driven also by a number of other factors such as use of CNIs.

Osteoporosis

The incidence of osteoporosis, bone fractures, and compromised mineral bone density appear to be reduced in CSw patients in both *late* [22] and *early* [18] withdrawal studies, although one study with *late* withdrawal did not demonstrate a significant difference [23]. Modern medical prophylaxis has likely reduced this complication in recent years.

Dyslipidemia and obesity

Serum lipid levels have been investigated in several studies of CS withdrawal after HTx. Significantly lower serum cholesterol and lower incidence of hyperlipidemia have been reported in CSw patients compared with CSm patients [15,17,34,43]. One retrospective study with *late* withdrawal, however, found an increase in serum cholesterol in CSw patients [29]. In terms of obesity, only one retrospective study demonstrated an increase in body weight in CSm compared with CSw patients [43], whereas both studies with *late* [34] and *early* withdrawal [17] have found no difference between CSw and CSm patients. It appears important to inform overweight patients that successful steroid weaning per se does not necessarily induce weight-loss.

Steroid weaning in CNI-free protocols

As CNIs might contribute to the development of some of the long-term complications attributed to CS use, such as hypertension, diabetes, and dyslipidemia [50,51], experience on the effects of CS withdrawal in CNI-free protocols is highly relevant. The feasibility of CS weaning in CNI-free patients might also differ from that of patients receiving CNI-based maintenance treatment, as biopsy-proven acute rejections have been reported to be more frequent in the CNI-free arms of both the SCHEDULE and the MANDELA study [52,53]. Similarly, the CECARI study found a trend toward more treated rejection episodes in the CNI-free arm [54]. In all three studies, maintenance regimen in the CNI-free arms consisted of everolimus and mycophenolate mofetil. Following randomization, CSs were either continued up to 12 months post-HTx or hereafter weaned at the discretion of the investigator [52], continued according to local practice [53], or left to the discretion of the treating physician [54] partly reflecting different timing of randomization to CNI-free regimen. Separate observations on patients undergoing CS tapering were not clearly described. To our knowledge, no dedicated studies have investigated CS weaning in CNI-free protocols, but further experience on CS weaning in this setting is necessary and this will hopefully be addressed in the future studies.

Eligibility for CS weaning

Previous experience suggests that some patient groups are less likely to tolerate CS withdrawal; however, uniform selection criteria for steroid withdrawal have not been established. No randomized trials of CS withdrawal after HTx have been conducted and as such, selection of candidates for steroid withdrawal might introduce bias. Reported selection criteria for CS withdrawal in current literature are heterogeneous

Table 4. Reported exclusion criteria/high-risk features in heart transplant patients, who were deemed ineligible for CS withdrawal.

High-risk features/exclusion criteria
Previous history of rejection [17,19,20,22,25,31,33,34,38]
Hemodynamic compromise [16,20,38]
Renal compromise [16,19,31,34]
Vascular rejection [16,31,34]
Retransplantation [19,26,34]
Multi organ transplantation [19,26,28,34]
Leukopenia [16]

Table 5. Reported features of patients who were less likely and more likely, respectively, to withdraw successfully from CS after heart transplantation.

Less likely to withdraw	More likely to withdraw
Previous history of rejection [32]	Benign history of rejection [32]
Medical noncompliance [38]	Male gender [14,32]
African American recipients [16,25]	Induction therapy [13,15]
Female gender [28,32]	
High pretransplant PRA [28]	
Longer ischemic time [28]	
Induction therapy [28]	

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[19,20,22,25,28,31,34,35], which severely challenges comparison of outcomes across studies. Generally, clinically stable patients with low immunologic risk appear to be selected for CS withdrawal. Proposed selection criteria and high-risk features in relation to CS withdrawal reported in available literature are presented in Table 4. African American patients have been found less likely to be successfully weaned from CSs [16,25], and male gender has been reported the only independent predictor of successful CS withdrawal [14]. Elboudwarej *et al.* [28] recently reported that patients maintained on CS treatment were more likely female and had pretransplant panel reactive antibodies (PRA) >10%, longer ischemic time, were more likely receiving induction therapy and supported with durable mechanical circulatory support prior to transplant. Other studies found

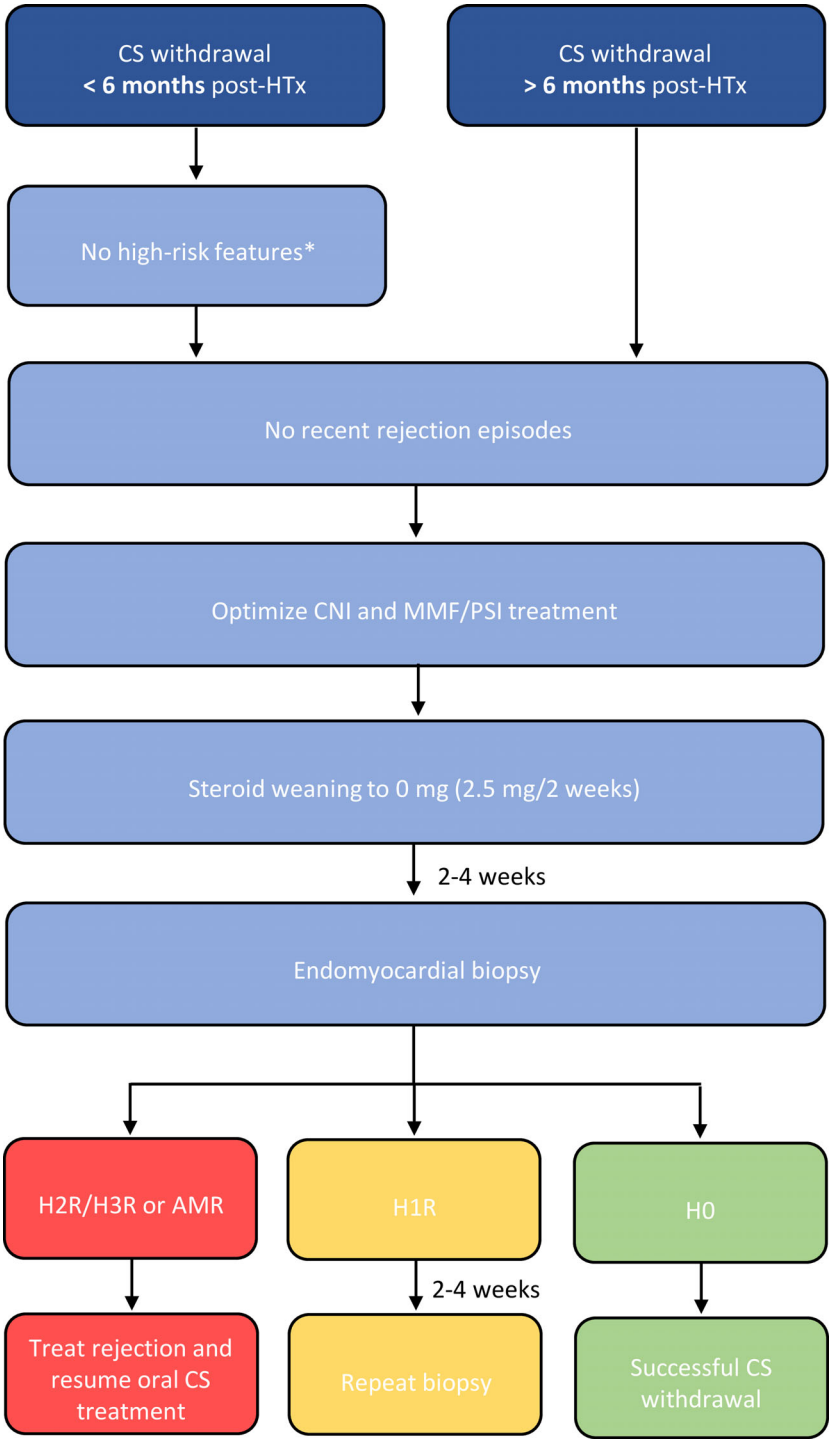

Figure 2 Proposed algorithm of CS withdrawal after heart transplantation. *See Table 4. AMR, antibody-mediated rejection; CNI, calcineurin inhibitor; HTx, heart transplantation; MMF, mycophenolate mofetil; PSI, proliferation signal inhibitor.

that aggressive CS avoidance was more successfully achieved when patients received induction therapy [13,15]. Reported features of patients who were able to withdraw from CS versus patients who were unable to withdraw from CS are listed in Table 5. Some consensus exists in terms of the definition of successful withdrawal, as this was widely defined by the absence of significant rejection [16–20,22,25,26,28,32,34–38].

Discussion

It remains challenging to identify patients from whom CS can be safely withdrawn. Further knowledge is needed with respect to clinical factors associated with increased risk and optimal timing. As clearly illustrated above, a randomized controlled trial is required to provide physicians and patients with adequate information on this topic.

It is remarkable that for patients in whom CS could not be completely withdrawn, no information about possible dose reductions was reported. It could clearly have provided important information if the cumulative CS dosages among patients and potential benefits of CS reduction had been assessed and this may be an objective of future studies. New molecular tools such as gene expression or cell-free DNA analysis might facilitate earlier, safe steroid withdrawal [55–58]. Currently, based on the available literature, it seems reasonable to suggest steroid weaning 6 months after HTx in patients without a high-risk profile including prior sensitization or several prior high-grade rejection episodes. Absence of significant allograft rejection after CS weaning should be confirmed as should stable graft function.

With the knowledge gathered from available literature, we have proposed an algorithm (Fig. 2) depicting a practical approach to patient selection for CS withdrawal after HTx including monitoring regimen and suggested definition of immediate successful withdrawal.

Limitations

Generally, the study populations of the studies evaluated in this review were small challenging statistical power and extrapolation. Importantly, inherent risks of retrospective and observational studies warrant cautious interpretation. Given that all existing studies are non-randomized, the risk of bias poses a very important issue in terms of interpretation. Also, existing studies are highly heterogeneous with respect to both study design, maintenance regimen, selection criteria for CS withdrawal, timing of withdrawal, and definition of successful withdrawal, which challenges comparisons and overall conclusions. The available studies did not include information about the presence of DSA or human leukocyte antigens (HLA) mismatching prior to steroid weaning. This could, however, have impact on the immediate success of CS weaning in terms of acute rejection, but potentially also on long-term risk of development of CAV. It is possible that the chance of successful CS weaning would increase if these measures were routinely included in the risk stratification, but this needs to be validated in the future studies.

Conclusion

Corticosteroid withdrawal appears to be feasible in selected HTx recipients without substantial risk of acute rejection. Current literature suggests that CS withdrawal is more successful when initiated beyond the first 6 months post-HTx, and an immune-privileged subset of patients appears more likely to tolerate CS weaning. Further refinement of withdrawal approach including optimal timing and selection criteria for successful CS withdrawal needs to be pursued in the future studies.

Authorship

All authors have contributed substantially to the submitted work through participation in design, performance, interpretation, or reporting. B Heegaard performed literature search and drafted the manuscript. LM Nelson and F Gustafsson have critically revised the manuscript and all authors approved the final submitted version of the manuscript.

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Conflicts of interest

BH and LMN have no relevant conflicts of interest to disclose. FG reports fees from Novartis, Pfizer, Orion, Abbott, Astra-Zeneca, Boehringer-Ingelheim, Alnylam, Ionis, and Bayer.

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