[Review article]

Heart transplantation in patients with previous malignancy. An overview

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Introduction A history of malignancy has been considered as a contraindication for heart transplantation. The number of patients with prior malignancy needing transplantation is increasing due to improved survival and to cardiotoxic cancer treatment. However, this reluctance for transplantation can be challenged by the already available results.

Methods A systematic literature search was performed in electronic databases. After exclusion of cardiac sarcomas, three case reports, thirteen series of which three are paediatric, two database searches and one article with specific design have been found. The larger series are of more recent origin. The study design of the manuscripts differed to some degree.

Results The preoperative profile and the postoperative results are reviewed. The preoperative profile includes demographics, interval between treatment of malignancy and transplantation, indication of transplantation and differences between patients with and without prior malignancy. An important observation is the increase of transplantation in patients with chemotherapy-related cardiomyopathy over time. The postoperative results show that hospital mortality and long-term survival do not differ significantly between patients with and without pre-transplant malignancy. This seems also to be true for post-transplant recurrence. The disease-free pre-transplant interval has a major effect on both outcomes. Patients with haematologic malignancies and after splenectomy have a worse prognosis. Use of LVAD (left ventricular assist device) as bridge-to-transplant and rapamycin as immune suppression, holds some promises.

Conclusions This review has some limitations since the published series are not comparable. It seems that transplantation in patients with prior malignancy can be justified in some cases, especially when the interval between malignancy and transplantation exceeds five years.

Keywords *Heart transplantation – malignancy – mortality – recurrence.*

INTRODUCTION

Heart transplantation is an effective treatment of end-stage cardiomyopathy (CMP)[1]. Older guidelines in the patient selection for heart transplantation have been drawn to a certain degree from experiences after renal transplantation[2]. More recent guidelines also deal with the difficult problem of pre-transplant malignancy (PTM)[3]. PTM has been considered as a contraindication for heart transplantation[4,5] since this condition has the potential to reduce life expectancy and could prohibit immune suppression after transplantation[6,7] because of an increased risk for recurrence[8-12]. This recurrence rate can be up to 21%, with almost 9 of 10 cases occurring within the first 5 years[13]. In coincidentally detected tumours, the recurrence rate is low which might be due to an early cancer stage[2]. On the other hand, the need for heart transplantation has increased for two reasons: first, an improved cancer survival, and, second, the use of cardiotoxic chemotherapy such as anthracyclines[14,15] and radiotherapy[8,16]. Chemotherapy-related CMP has been reported in 10 to 27% of cancer survivors. This condition progressed in 2 to 4% to end-stage heart

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failure[16]. Any chemotherapeutic agent can induce myocardial damage but anthracyclines are documented most extensively. These agents inhibit topoisomerases and DNA polymerases, causing DNA fragmentation. Cardiomyocytes are damaged by free oxygen radicals and lipid peroxidation. These effects are dose-dependent: a quarter of patients receiving a cumulative dose of 550 mg/m² develop clinically relevant myocardial damage. Prior heart disease, advanced age and association with other agents such as trastuzumab and taxanes add to this risk for developing CMP[17,18]. Furthermore, radiation-induced myocardial fibrosis has become the second cause of death in patients with a cured Hodgkin's disease. Valvular and coronary disease can also be the result of radiation[17]. The cardiotoxic effect of chemotherapy can be reduced by beta-blocking agents and angiotensin-converting enzymes. Chelating agents such as dexrazoxane might also have a positive effect. Lowering of the radiation dose and volume and use of shielding devices in patients undergoing radiation of the mediastinum or the left breast can also lower the cardiac side effects[18]. Detection and follow-up of cardiotoxic effects can be performed by serial examination by ECG, echocardiography and cardiac troponin. Classical lifestyle changes can also be helpful in the prevention of heart disease[17]. If, in spite of these measures, end-stage heart failure develops, heart transplantation is one of the viable options[15,19]. LVADs can be used as bridge therapy in patients with PTM if the interval between the malignancy and the need for heart transplantation is two years or less. This can gradually expand the criteria of listing for transplantation by increasing the interval[20]. Moreover, LVAD, if implanted electively, has a similar survival and quality of life, compared to transplantation, but without the need for immune suppression and hence, reactivation of the cancer.

Few of these relatively young cancer survivors with end-stage CMP received heart transplantation before 1995[1]. The reasons were the reluctance to transplant patients with PTM because of the risk of recurrence and a shortage of donor hearts[1,21]. However, the number of patients with PTM who received a transplant increased and varied between 0.9 and 6% in more recent series[7,9-13,16]. In one series, PTM was present in 10/67 or 14.9% of the patients referred for transplantation but only 2/10 received a donor heart. In this group, investigation for cancer was more thorough than in usual clinical practice[21]. The main questions for this review are: what are the post-transplant results of PTM patients and of patients with chemotherapy-related CMP? In which patients with prior malignancy and end-stage heart failure is transplantation justified? What are possible risk factors for adverse events after heart transplantation in these patients?

METHODS

For this purpose, a systematic literature search was performed using the terms: "heart transplantation AND malignancy* OR cancer" through the ISI Web of Knowledge. There were 707 hits and 124 articles were selected on title. After exclusion of series including cardiac tumours and malignancy following cardiac surgery, three case reports[6,14,22], ten series[1,8,9,11-13,15,16,19,23], two database searches[7,10] and one article with a specific design were found[17]. Three additional series were committed solely to paediatric patients[24-26]. The most recent of these series included 7,189 children, who were transplanted between 1987 and 2011. There were 107 survivors of a prior malignancy. The two other series were much smaller. A secondary search through the references of the included manuscripts did not result in more articles. Results of lung transplantations in reports with heart and/or lung replacements were excluded. All case reports have been published before 1995. Series which include statistical analysis appeared from 1995 onwards. Three of these manuscripts were published before 2000 and six appeared after 2010. All reports are retrospective, and the study design differed. Preoperative profiles and postoperative results were analysed.

RESULTS

Preoperative profile

The preoperative profile (table 1) includes patient age at transplantation, gender, disease-free interval, type of malignancy and indication for transplantation. The mean patient age varied from 6 years [24] to 52 ± 12 years[6]. Some series included adult as well as paediatric cases[1,8,9,11]. The percentage of male gender in the larger series varied between 34% [10] and 76% [7]. This could be related to differences in inclusion of gender-specific cancers. The mean "disease-free interval", i.e. the interval between the treatment for cancer and the actual heart transplantation varied between 2.8 years [9] and 26 years [23]. In one series, the effect of the disease-free interval on postoperative survival was explicitly studied[12]. The type of malignancy varied but haematologic malignancy was prominently present in several series[1,8,12,16]. Breast cancer (31%) was also a common malignancy[16]. One series was entirely based on lymphomas and focused on the effect of the type of lymphoma and of splenectomy[15].

The indication of heart transplantation differed between series. Dilated, congestive or idiopathic CMP was mostly the common reason for transplantation in four series: up to 1/2 to 2/3 of the patients[7,9,12,23]. Chemotherapy-related CMP was the most important reason for transplantation in other series[1,8,13,15]. Furthermore, a

Table 1 Pre-transplant patient characteristics

Reference	N	Age (y)	Male	Type	Indic.	Interval (y)
(1)	11	26 ± 17 y	63%	haem (6/11)	CCMP (6/11)	9.6
	42			haem (18/42)	CCMP (20/42)	
(7)	1117	52 ± 12	76%	all	DCMP	
(8)	9	31 ± 20 y	45%	mixed	CCMP (all)	11 ± 7
(9)	20	55	75%	haem (5/20)	DCMP	2.8 (0-20)
(10)	453	44	34%		CCMP	
(12)	74	35 ± 18	53%	mixed	DCMP (55/74)	
(13)	13	47	46%		CCMP (6/13)	6.2
(14)	7	12-47 y	71%	haem (6/7)		2-20y
(15)	16	41 ± 15	75%	Hodgkin	ICMP (8/16)	15 ± 9
	18	42 ± 17	61%	NHL	CCMP (13/18)	10 ± 9
(16)	232	46	36%	haem (49%)	CCMP	
(23)	9	46 ± 11	33%	lymphoma	DCMP (5/9)	26
(24)	17	6		all	CCMP	9.2 (0.4-15.2)
(25)	36	14.8		haem	CCMP	12

CCMP: chemotherapy-related cardiomyopathy, DCMP: congestive and dilated CMP: haem: haematological, indic. main indication for transplant, ICMP: ischaemic CMP (between brackets the number of patients for this specific indication), n: number, NHL: non-Hodgkin lymphoma, Y: years.

considerable increase in referral for chemotherapy (adriamycin)-related CMP was observed between 1990 and 2010 while transplantation for CMP of other origin remained constant[10]. This observation was confirmed in a second report: 38% of the patients with chemotherapy-related CMP were referred in the period 2000-2004, the remaining 62% in the period 2005-2008 with 23% in 2008 alone[16]. Referral for ischaemic CMP varied but was never the major indication for transplantation.

There were some confounding factors concerning the effect of the type of CMP on postoperative results. In most series, patients with PTM and chemotherapy-related CMP were younger compared to patients with other types of CMP[10,13,16]. In all these series, PTM patients were more often of female gender and had a lower BMI[7,13,16,19]. Cardiac output in PTM patients was equal[7] or lower[10], while need for LVAD support was equal[16] or less[7,10]. In most series, co-morbid conditions (increased serum creatinine, hypertension, diabetes, pulmonary hypertension and arrhythmias) were less present in PTM patients[10,16]. These differences can be related to a more strict pre-transplant selection for patients with PTM.

Postoperative survival and its predictors

The postoperative results are given in table 2, except for the case reports and the smallest series. These include hospital mortality, survival at 1, 2, 5 and 10 years as well as recurrence of malignancy. (1) Hospital mortality varied between 0% and 33% [1,6,11,19,22,23], but these data came from case reports and small groups, which explain the observed variation. One larger series suggests that hospital mortality after transplantation was similar between chemotherapy-related and other non-ischaemic CMP[16]. (2) One-year overall survival in older small series varied between 57% [14] and 100% [1] and seems similar in patients without PTM[9,14]. These data, however, must be treated with caution since most series had less than 10 patients. In a more recent and larger series[16] including 232 patients, a one-year survival of 86% was observed for patients with chemotherapy-related CMP, compared to 87% of other transplant patients. Graft failure was responsible for half of the fatalities, followed in descending order by acute rejection, infection, multiple organ failure and malignancy. The pattern was similar for both PTM and non-PTM patient groups. In this series, 9 predictors for one-year mortality could be identified of which the most important were need for LVAD, need for total artificial heart, need for temporary circulatory or ventilator support and history of dialysis. The type of CMP had no significant effect on one-year survival[16]. In a smaller series, consisting solely of patients with prior lymphoma, Hodgkin's disease and prior splenectomy had a negative effect on one-year survival[15]. (3) Survival at two year varied between 82% and 100% and did not differ between patients with adriamycin-related CMP and other patients[1,6,10]. (4) Five-year survival was lower in PTM patients (50% v. 70%) in an older small series[9]. In larger and more recent series, 5-year survival of PTM

patients was between 70 and 80% and similar to that of other transplant patients[10,16]. (5) In one series, ten-year survival is similar for patients with chemotherapy-related CMP (63%) and other patients (62%) undergoing transplantation[13]. A modest advantage for patients with adriamycin-related CMP was observed, with an adjusted hazard ratio of 1.28[10].

In summary, short- and long-term post-transplant survival in PTM patients was similar to that of other patients[1,7,10]. In contrast, non-malignancy related factors such as indicators of cardiac, pulmonary and renal dysfunction were identified as independent predictors of 5-year survival[16]. However, two malignancy-related factors also showed clear effects. First, a malignancy-free interval of less than one year had a significantly lower five-year survival compared to a longer interval (less than 60% v. more than 75%) but this group contained also lung transplant patients in whom lung cancer was coincidentally found at pulmonary transplantation[12]. Second, the type of malignancy had also an effect. Patients with prior haematologic malignancies had an increased post-transplant mortality[6,8], especially in one series dealing exclusively with pre-transplant lymphoma. The hazard ratio was 6 in patients with Hodgkin's disease who also underwent splenectomy[15]. The cause of death did not differ: mortality in PTM patients, due to recurrence and metastasis, was similar to the mortality in other transplant patients[1,8]. Cardiovascular causes for mortality were also similar (21 v. 23%) for both types of patients[10].

Table 2 also indicates that there is probably no real effect of age on survival: the survival at 1, 2, 5 and 10 years does not differ considerably between paediatric patients[24-26], series of patients with a mean age over 50 years [7,9] and the series with a median age between 20 and 50 years [1,8,10,12-16,23]. One should bear in mind that these are the effects of the median age of groups, not of individual ages. Age over 60 years has been identified as a risk factor in only one series[7].

Postoperative recurrence of malignancy

The recurrence rate of malignancy is also important. Few or no recurrences were observed in small series with different types of cancer[1,8,13,14,16,19]. Second primary tumours after heart transplantation were also uncommon[1,14,15,19]. As for mortality, the disease-free interval had a clear effect: if this interval was less than one year, the recurrence rate was 63%, if it was 1 to 5 year, it was 26% and for an interval of more than 5 years, it was only 6% [12]. The indication for transplantation also had an effect: recurrence of malignancy was significantly higher in patients with chemotherapy-related CMP compared to other transplant patients (5% v. 2%), but this had no

Table 2 Post-transplant outcomes: hospital mortality, survival rates and cancer recurrence

Reference		Hosp. mort.	1-year	2-year	5-year	10-year	CA
(1)		9%	100%		82%		9%
(7)	PTM		84% (est)	80% (est)	73% (est)		
(7)	no PTM		84% (est)	80% (est)	76% (est)		
(8)		11%	7/8			6/8	12.5%
(9)		10%	75%*		50%*		15%
(10)			90%	85%*	75%*	65%	
(12)	I				55%*		63%
(12)	II				75%*		26%
(12)	III				80%*		6%
(13)						63%	0%
(15)	AL	3%	77%	64%**	64%	50%	
(15)	HO		69%		54%	31%	
(16)			86%	79%**	71%		5%
(24)			100%	92%	60%		
(25)					74%	67%	
(26)	PTM		90.6%		80.3%	65.0%	13.0%
(26)	no PTM		84.4%		73.8%	57.7%	5.4%#

AL: all lymphomas, CA: cancer recurrence, (est): estimated from survival curve, HO: Hodgkin only, hosp. mort: hospital mortality, * % estimated from survival curves ** at 3 years, # de novo cancer, I: interval < 1 year, II: interval between 1 and 5 years, III: interval > 5 years.

effect on survival[16]. Post-transplant malignancy could be related to changes in the immune system. However, there was no need to alter the regimen of immune suppression in patients with PTM[6]. There was a tendency to increased infection rates in PTM patients[6], especially after longer follow-up[13]. In one recent larger series, this difference was significant, but this had no effect on survival[16]. No increase of rejection[6,14] has been observed while the immune suppression was similar[13]. In one recent larger series, a lower 1-year freedom of rejection was observed in PTM patients[16].

Table 3 offers an overview of factors that have no, a likely increased (conflicting reports, factors considered as relative contraindications in the ISHLT guidelines) or a definitively increased risk (high risk or hazard ratio, several reports indicating the same outcome or factors considered as absolute contraindication) for cardiac transplantation, compared to patients in whom these factors are absent. High age, active malignancy, especially when it is in an advanced stage or co-morbid conditions all carry a certain risk. Multiple myeloma is considered as a contraindication for renal transplantation. This will certainly also apply for cardiac transplantation[27]. It is, however difficult to separate confounding factors and hence to classify them as definitive risk or not: in one small series, for example, mediastinal radiotherapy is associated with poor outcome, but all patients had a prior lymphoma, which is also associated with inferior post-transplant results[23].

DISCUSSION

Older reports, based on cases and small series indicated that heart transplantation in patients with prior malignancy could be successful in selected patients[6,8,14]. More recent reports are derived from larger databases[7,10,16] and show that long-term outcome after heart transplantation of patients with PTM or chemotherapy-related CMP is similar to transplantation for other types of CMP, without major changes in the immune suppression regimen[10,13,16]. This observation makes transplantation feasible in patients with end-stage heart failure and previous malignancy or chemotherapy-related CMP. Some remarks have to be made, however.

First, survival rate after cancer treatment increases, and with it, the occurrence of chemotherapy or radiotherapy-related CMP. While transplantation for adriamycin-related CMP is increasing, transplantation for other reasons remains constant[8,10,11,16]. Moreover, it remains to be seen whether more modern chemotherapeutic regimens are less cardiotoxic. Hence, the number of cancer survivors with end-stage heart failure will also increase. Overload of the right ventricle and need for a right ventricular assist device might be due to a chemotherapy-related CMP[8,16]. Radiotherapy of the chest is a second possible cause for CMP since it can be held responsible for the development of myocardial fibrosis. End-stage heart failure can develop, even after successful treatment of radiation-induced coronary or valve disease[19].

Table 3 Factors associated with reduced survival

Factor	No increased risk	Risk likely	Definitive risk
Tumour type, interval	localized prostate CA (27) in situ bladder CA (27) skin CA (7) high interval (> 10 years)	interval < 1year if expected 5-y survival > 70% (9,11)	no cure achieved or metastasis detected (3) multiple myeloma (27) HD with splenectomy (15)
Type CMP	adriamycine related CMP (1,6,10,13,16)	CCMP (9)	end-stage heart failure due to congenital heart disease (7)
Need for MCS		pulsatile or CF LVAD (7,16)	total artificial heart (16)
Demographics, co-morbidity	age < 70 and diabetes without end-organ damage (3) male gender (7)	age > 70 after careful selection (3) black race (7) diabetes with end-organ damage or poorly controllable glycaemia; GFR< 40 ml/min; PAD limiting post-transplant rehabilitation (3)	BMI > 30 kg/m^2; clinical severe cerebrovascular disease (3) active smoking cytomegaly virus positive new onset or history of dialysis or on ventilator (7,16)

BMI: body mass index, CA: cancer, CCMP: chemotherapy-related cardiomyopathy, CF: continuous flow, GFR: glomerular filtration rate, HD: Hodgkin's disease, LVAD: left ventricular assist device, MCS: mechanical ventilator support, PAD: peripheral artery disease.
No increased risk: all reports indicating no increase in hazard ratio/risk ratio; Risk likely: conflicting reports and/or hazard ratio below 2; Definitive risk: several reports indicating an increased risk and/or hazard ratio above 2.

Second, patient selection is a major determinant of outcome after heart transplantation. An important factor is the disease-free interval, which is inversely related to post-transplant tumour recurrence, tumour mortality and mortality for all causes[12]. The optimal disease-free interval is not known[10] and guidelines can differ according to the recommending society, the type and the stage of the malignancy[27], at least for renal transplantation. This also applies to cardiac transplantation. The disease-free interval might be one year if the expected 5-year survival for a given patient with a previously treated tumour is at least 70% [9,11], but no arbitrary period should be used[3]. Good postoperative results in patients with previous malignancy, who underwent more routine operations such as CABG, have been achieved. Such results required a malignancy-free interval of at least two years, in a condition where no immune suppression is necessary[28,29]. Even a cardiac operation in patients with simultaneous cancer and heart disease could be defended, since the cardiac condition can be more lethal in the short term. However, a more strict attitude should be advocated for heart transplantation in patients with PTM: in such patients, a complete remission of PTM for at least 2 and probably 5 years must be ensured[13,19]. Hence, candidates for heart transplantation and PTM need careful examination[8,10]. This is illustrated by the discovery of malignancy in 10 of 67 patients referred for transplantation after thorough examination. Of these patients, 8 were rejected for transplantation[21]. Another factor in the decision-making is the type of PTM. Haematological malignancies have a worse outcome[9,12]. Splenectomy in patients with prior Hodgkin's disease resulted in increased mortality, while patients without prior splenectomy had a survival similar to the "general" transplant group[15]. Radiotherapy for lymphoma also seemed to result in poor outcome after transplantation for RT-related CMP[23].

Third, immune suppression does not seem to enhance the recurrence of the malignancy if its treatment has been successful[1,8,15], although an increase was observed in older patients and in patients treated by mono- or polyclonal antibodies[9]. Post-transplant infection and malignancy were more common in patients with chemotherapy-related CMP, but without affecting survival. This might be due to a long-lasting effect of chemotherapy on immunity[16]. Mammalian target of rapamycin (mTOR) inhibitors have been introduced recently in the post-transplant immune suppression regimens. Patients with hepatocellular carcinoma who received a liver transplant had a better survival and lower tumour recurrence if a calcineurin inhibitor was replaced by an inhibitor of mTOR[30]. Tacrolimus, as part of a triple immune-suppressing regimen, also shows better results in terms of rejection and survival[31] as well as in terms of freedom from malignancy after transplantation[32]. It seems that an improved immune suppression by inhibitors of mTOR is not at the cost of an increased risk of cancer[33].

Fourth, LVAD devices have been used for destination therapy as well as for bridge-to-transplant. The first-generation pulsatile-flow devices were large and prone to mechanical failure. Continuous-flow devices are smaller and more durable. These require less extensive surgery. These devices can be used in UNOS status 1A/1B patients as destination treatment and prolong survival, with improvement of quality of life. Serious complications have been documented such as stroke, thrombosis of the device, infection of the lead and right ventricular failure[34]. There is little difference between modern devices[35]. The benefit of LVAD as bridge-to-transplant seems uncertain, however. The risk ratio for 1-year mortality after transplantation in patients who had a chronic continuous-flow device was 1.48. For a chronic pulsatile-flow device, the ratio was 1.34. However, for those patients who survived the first year after transplantation, the risk ratio for patients in whom chronic pulsatile has been implanted decreased to 0.85 [32]. In other series, no significant effect was found[7]. Implantation of LVAD is not encouraged in patients with stable UNOS status 1, who are stable on i.v. inotrope therapy: not only early but also long-term post-transplant survival is reduced. Impaired cellular immunity and allosensitization could be reasons for this observation. However, the indication of LVAD and the survival to transplant were not known in this series and only pulse-flow devices were studied[36]. Continuous flow LVAD also show some risk for stroke. Once such an event has occurred, this is considered as a major contraindication for subsequent cardiac transplantation[37].

Some questions remain for patients with PTM or chemotherapy-related CMP who are dying unnecessarily of end-stage heart failure. Is it prudent to perform heart transplantation in patients with PTM if donor hearts are scarce[1,8,38]? A similar question can be asked for cardiac patients older than 70 years who need transplantation. Although life expectancy might be lower, in comparison with younger patients, the use of older donor hearts might alleviate the allocation problem[3]. The treatment of patients with this complex condition has become a team decision since it is not only difficult to define "end-stage heart failure" but also to identify patients with prior malignancy who still can benefit from heart transplantation. This requires collaboration between cardiologists and oncologists. The most recent recommendations[23] have a class I **level**, with a level of evidence C or expert opinion. However, a multicentre registry is needed and should include the type and stage of the tumour, the type of treatment with focus on cardiotoxic chemotherapy and radiation on the heart

if applied, and response of the malignancy, as well as the malignancy-free interval before transplantation. The latter could serve as a measure for chance of cure. This important parameter is lacking in the more recent, larger series but should be included as has been done for patients undergoing more routine cardiac operations[28].

This paper shows some limitations and strengths. The included studies are universally retrospective and differ in design. This precludes a meta-analysis. The included series vary considerably in size and are not always comparable. Extraction of data from large databases rely heavily on the training of the extractors. Details of chemotherapeutic agents (type and doses) and of radiotherapy (doses applied on the heart) are lacking. For all these reasons, drawing strong conclusions is difficult. Furthermore, some series include patients with PTM, other include patients with chemotherapy-related CMP, which is not entirely the same. Classifying factors according to: (a) no increased risk, (b) no definitive risk, and (c) definitively increased risk, is a matter for debate: most factors (such as elevated serum creatinin) can be expressed as a continuous variable, making classification by defining cut-off values somehow arbitrary. Moreover, by studying one factor, for instance, adriamycin-related CMP, other confounding factors such as age, type of tumour treatment and the presence of co-morbid conditions can differ[10,17,23], which makes interpretation difficult, and sometimes contradictory. Some series suggest that the presence of PTM does not affect survival after cardiac transplantation[9,10,14,16,24,25] but how patients were selected has to be taken into account in the interpretation of these findings. Nevertheless, the major findings are consistent and point to a feasibility of cardiac transplantation in patients with end-stage heart failure and a prior malignancy. Moreover, recent reports involve larger multicentre series including a longer follow-up with 10-year survival rates. Inclusion of different ethnicities and nationalities from larger databases make the findings generally applicable and could eliminate sources of bias. A registry including the necessary details concerning demographic parameters and tumour treatment modes remains invaluable.

CONFLICTS OF INTERESTS: none to declare.

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