STUDY

Incidence and Clinical Predictors of a Subsequent Nonmelanoma Skin Cancer in Solid Organ Transplant Recipients With a First Nonmelanoma Skin Cancer

A Multicenter Cohort Study

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Objective: To compare the long-term risk of primary nonmelanoma skin cancer (NMSC) and the risk of subsequent NMSC in kidney and heart transplant recipients.

Design: Partially retrospective cohort study.

Setting: Two Italian transplantation centers.

Patients: The study included 1934 patients: 1476 renal transplant recipients and 458 heart transplant recipients.

Main Outcome Measures: Cumulative incidences and risk factors of the first and subsequent NMSCs.

Results: Two hundred patients developed a first NMSC after a median follow-up of 6.8 years after transplantation. The 3-year risk of the primary NMSC was 2.1%. Of the 200 patients with a primary NMSC, 91 (45.5%) had a second NMSC after a median follow-up after the first NMSC of 1.4 years (range, 3 months to 10 years). The 3-year risk of a second NMSC was 32.2%, and it was 49 times higher than that in patients with no previous NMSC. In a Cox proportional hazards regression model, age older than 50 years at the time of transplantation and male sex were significantly related to the first NMSC. Occurrence of the subsequent NMSC was not related to any risk factor considered, including sex, age at transplantation, type of transplanted organ, type of immunosuppressive therapy, histologic type of the first NMSC, and time since diagnosis of the first NMSC. Histologic type of the first NMSC strongly predicted the type of the subsequent NMSC.

Conclusions: Development of a first NMSC confers a high risk of a subsequent NMSC in transplant recipients. Intensive long-term dermatologic follow-up of these patients is advisable.

Arch Dermatol. 2010;146(3):294-299

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PATIENTS UNDERGOING SOLID organ transplantation are at increased risk for nonmelanoma skin cancers (NMSCs), mostly squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), and various risk factors have been well documented.[1-3] Incidence rates of posttransplantation NMSC differ according to geographic latitudes; in Italy, they are approximately 5% after 5 years and 10% after 10 years.[4] Higher rates have been observed in northern Europe (10% after 10 years and 40% after 20 years) and in Australia (45% after 11 years and 70% after 20 years).[5,6] The reported average time to the development of NMSC is estimated to range from 4 to 9 years after organ transplantation.[1-7] Male sex, older age at transplantation, and longer follow-up after transplantation were independently associated with the onset of NMSC.[4] Other predictors of NMSC after organ transplantation are skin phototypes I to III according to the Fitzpatrick scale, an excessive sun exposure history, aggressive immunosuppressive protocols, cumulative dosages of immunosuppressive drugs, and genetic factors.[5,8-13] All of these studies investigated only the first NMSC after transplantation, but the risk of a subsequent NMSC after the diagnosis of a first NMSC is well recognized in daily clinical practice.

A comprehensive meta-analysis[14] in nonimmunosuppressed patients re-

ported a 3-year cumulative risk of 35% to 60% of a subsequent NMSC after a first NMSC of any type, BCC or SCC, with at least a 10-fold increase in incidence compared with the incidence of first tumors in the general population. In most patients, the histologic type of the subsequent NMSC was the same as that of the first NMSC.[14] In a recent study,[15] patients with both BCC and SCC were found to be at decreased risk of subsequent BCC compared with patients with BCC only. Male sex, older age, excessive recreational sun exposure, and the number of tumors at first consultation were considered independent predictors of the subsequent NMSC.[14,15] In solid organ transplant recipients, Euvrard et al[16] reported a 5-year cumulative risk of 71% of developing a second NMSC after a first index SCC. In this study, independent predictors of subsequent NMSC were multiple skin cancers at first examination, blue eyes, fair skin, blond hair, and transplantation before 1984. Minimization of immunosuppressive therapy after diagnosis of the first NMSC seemed to be protective.[16] To our knowledge, no studies have compared the risk factors of the first and subsequent NMSCs in transplant recipients. Better understanding of the timing of and the risk factors for a subsequent NMSC in solid organ transplant recipients would help in the design of a more rational follow-up approach to these patients.[17] The aim of this study was to analyze the incidence rates of, the timing of, and the risk factors for a second NMSC occurring after a first NMSC in a cohort of Italian kidney and heart transplant recipients.

METHODS

This was a partially retrospective cohort study. Between January 1, 1993, and December 31, 2008, 1934 consecutive kidney and heart transplant recipients at 2 Italian transplantation centers (Verona and Bergamo) were regularly followed up after transplantation. All of the patients were seen regularly at the outpatient nephrologic or cardiosurgical clinic, and those with cutaneous lesions were also seen by a dermatologist. In addition, every effort was made to collect information on any dermatologic diagnoses made outside the study centers. Detailed clinical records were available for all participants. Patients who had received the graft before the beginning of the study (367 of 1934 patients [19.0%]) were interviewed if they had undergone surgery for NMSC, and an accurate review was performed of their medical history, of the transplant registry, and of all the available clinical records. The diagnosis of NMSC was always confirmed by histologic analysis. Only patients with BCC and SCC were included in the present study. Thirteen patients, 9 with Bowen disease and 4 with keratoacanthoma, were excluded. For each patient, the following data were collected: age, sex, date of transplantation, type of immunosuppressive therapy, date of the first and second NMSCs (if any), and date and cause of loss from follow-up. For patients with NMSC, skin type, eye and hair color, and the presence of cutaneous keratotic lesions were also recorded. The NMSC had to meet 2 criteria to be considered new: the site of the new cancer could not be contiguous to a scar, which could represent a previously treated NMSC site, and it had to occur at least 3 months after treatment of the first NMSC. Patients with recurring NMSC at the site of a previous surgical procedure were not included in the present study. Seven patients developed the second NMSC within 3 months of the first NMSC and were excluded. Informed consent was provided by all the participants, and the study was approved by the local ethics committee.

IMMUNOSUPPRESSIVE THERAPY

Induction therapy and maintenance immunosuppressive therapy varied by medical center and transplanted organ. Induction was usually performed with anti–interleukin 2 receptor monoclonal antibody (Simulect; Novartis AG, Basel, Switzerland) or antithymocyte immunoglobulins (bioMérieux Italia s.p.a., Bagno a Ripoli, Italy or Genzyme Corp, Cambridge, Massachusetts). Long-term maintenance immunosuppressive therapy, either alone or in various combinations, included azathioprine (1.0-2.5 mg/kg/d), cyclosporine (3-9 mg/kg/d), oral methylprednisolone (5-10 mg/d), oral tacrolimus (0.15-0.30 mg/kg/d), mycophenolate mofetil (2 g/d), and, with increasing frequency, sirolimus or everolimus.[11-13] Acute rejection was usually treated with pulsed methylprednisolone (0.5-1.0 g/d for 3 consecutive days). Corticosteroid-resistant acute rejection was treated with plasmapheresis, muromonab (anti-CD3 monoclonal antibody), or antithymocyte immunoglobulins.[14-16,18,19]

STATISTICAL ANALYSIS

Cumulative incidences of the first and second NMSCs were computed. Concerning the first NMSC, the number of person-years was computed between the date of transplantation (used as the opening date) and the date of NMSC diagnosis (considered to be the end point), the patient's death, loss to follow-up, or the end of the study (December 31, 2008) (used as closing dates). When evaluating the second NMSC, the number of person-years was computed between the date of the first NMSC diagnosis and the date of the second NMSC diagnosis (considered to be the end point), the patient's death, loss to follow-up, or the end of the study (December 31, 2008). Kaplan-Meier survival curves were initially constructed. Subsequently, for estimates of potential prognostic factors, a Cox proportional hazards regression model was applied. An assumption of the Cox regression method is that the hazards for different strata of each independent variable are proportional over time. This assumption was verified using a graphical method. The survival curves for the variable strata were plotted on a log-log scale. If the curves were approximately parallel, then the assumption of the proportional hazards was considered satisfied. A backward stepping procedure with preassigned $P = .05$ for removal of variables was used.[20] Statistical analyses were performed using a statistical software package (Stata, version 10; StataCorp LP, College Station, Texas).

RESULTS

The characteristics of the study population are reported in **Table 1**. There were 1344 men and 590 women; 1476 patients were renal transplant recipients and 458 were heart transplant recipients; the mean (SD) follow-up time since transplantation was 9.2 (6.6) years (median, 8.0 years; range, 1.0-33.0 years). Two hundred patients (146 renal transplant recipients and 54 heart transplant recipients) developed a first NMSC after a mean (SD) follow-up of 8.4 (6.1) years and a median follow-up of 6.8 years (range, 1.5-15.2 years). No differences existed between renal and heart transplant recipients. Eleven of 200 patients (5.5%)—9 renal transplant recipients and 2 heart transplant recipients—had 2 or more NMSCs at the time of the diagnosis of the first NMSC. Two renal transplant recipi-

Table 1. Characteristics of the Study Population

Characteristic	Renal Transplant Recipients (n=1476)	Heart Transplant Recipients (n=458)
Sex, No. M/F	974/502	370/88
Age at transplantation, y		
Mean (SD)	44.4 (16.7)	50.1 (15.1)
Median (range)	43.8 (20.1-60.8)	53.4 (26.3-65.9)
Posttransplantation person-years, No.	14 675	4214
Follow-up after transplantation, y		
Mean (SD)	9.4 (7.0)	8.7 (4.8)
Median (range)	8 (1.0-33.0)	9 (1.0-20.0)
Immunosuppressive therapy, No. (%)		
1 Drug + prednisolone	664 (45.0)	279 (60.9)
2 Drugs + prednisolone	812 (55.0)	179 (39.1)
Censored observations, No.		
Lost to follow-up	75	5
Death	133	49
Chronic rejection of the graft	118	45

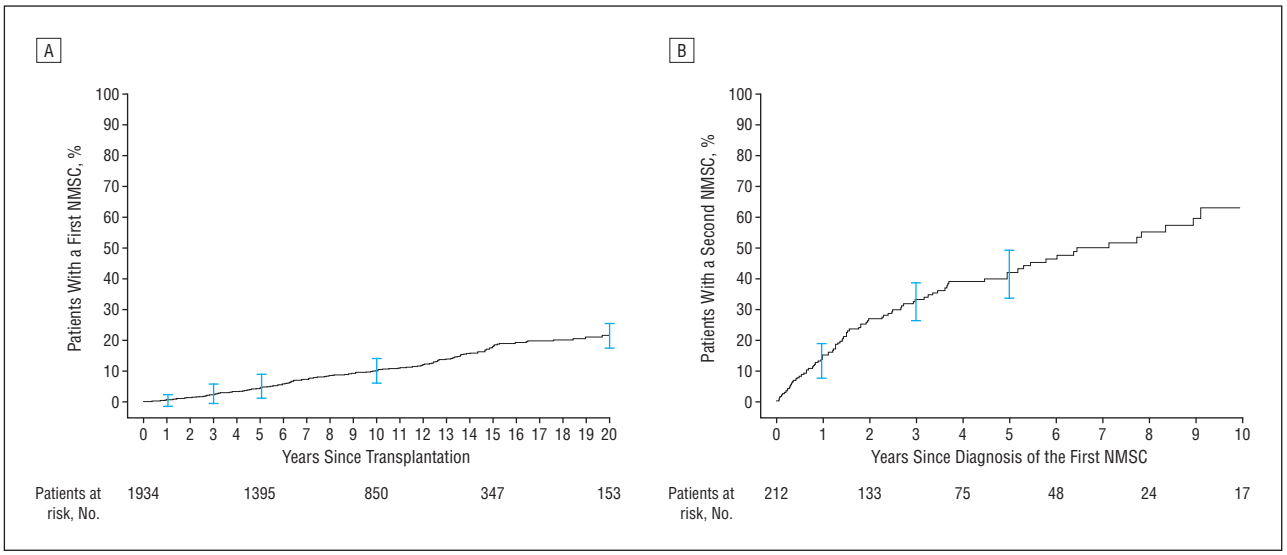

Figure 1. Cumulative incidences of the first (A) and second (B) nonmelanoma skin cancers (NMSCs) in the study population. Vertical bars indicate 95% confidence intervals.

ents died of metastatic SCC. The cumulative incidence of the first NMSC since transplantation increased progressively from 0.4% after 1 year to 21.3% after 20 years (**Figure 1**A). The 3-year risk of the primary NMSC was 2.1%. Of the 200 patients with a primary NMSC, 91 (45.5%) had a second NMSC after a mean (SD) follow-up since the first NMSC of 2.2 (2.1) years and a median follow-up of 1.4 years (range, 3 months to 10 years). The cumulative incidence of the second NMSC was much higher and also increased over time from 14.4% after 1 year to 61.5% after 10 years (Figure 1B). The 3-year risk of a second NMSC was 32.2%. Patients with a first NMSC had a probability of developing a second NMSC after 1, 3, 5, and 10 years of 33, 49, 10, and 6 times higher than that in patients with no previous NMSC. **Table 2** describes the clinical characteristics of patients with a first NMSC and of those with a second NMSC. The head and neck were the most commonly affected sites. Most patients with NMSC belonged to phototypes III and IV according to the Fitzpatrick scale. When statistical analyses were stratified according to the transplanted organ, no substantial differences were observed. **Table 3** shows the risk factors for the onset of the first and second NMSCs calculated using the Cox proportional hazards regression model. Older age at the time of transplantation and male sex were independently related to the first NMSC. The second NMSC was not related to sex, age at transplantation, type of transplanted organ, type of immunosuppressive therapy, length of follow-up at the diagnosis of the first NMSC, and type of the first NMSC. In a further analysis that considered the subsequent BCC and SCC as separate end points, the histologic type of the first NMSC strongly predicted the risk of a subsequent NMSC of the same type (Table 3 and **Figure 2**). Further analysis taking into account the skin site of the first cancer (photo exposed vs non–photo exposed), phototype, eye and hair color, and the presence of actinic keratoses at diagnosis of the first NMSC gave no statistically significant results (data not shown). Types and dosages of immunosuppressive drugs were not changed after diagnosis of the first NMSC.

Table 2. Clinical Characteristics of Transplant Recipients With a First NMSC and With a Second NMSC

Characteristic	Patients With a First NMSC (n=200)	Patients With a Second NMSC (n=91)
Follow-up at diagnosis of NMSC, y		
Mean (SD)	8.4 (6.1)[a]	2.2 (2.1)[b]
Median (range)	6.8 (1.5-15.2)	1.4 (0.2-10)
Type of transplanted organ, No. (%)		
Kidney	146 (73.0)	71 (78.0)
Heart	54 (27.0)	20 (22.0)
Type of NMSC, No. (%)		
SCC	109 (54.5)	50 (54.9)
BCC	91 (45.5)	41 (45.1)
Site of NMSC, No. (%)		
Head and neck	117 (58.5)	50 (54.9)
Trunk	44 (22.0)	16 (17.6)
Upper arms	34 (17.0)	14 (15.4)
Lower legs	5 (2.5)	11 (12.1)
Immunosuppressive therapy, No. (%)		
1 Drug + prednisolone	105 (52.5)	35 (38.5)
2 Drugs + prednisolone	95 (47.5)	56 (61.5)
Eye color, No. (%)		
Black or brown	108 (54.0)	47 (51.6)
Blue or green	92 (46.0)	44 (48.4)
Hair color, No. (%)		
Black or brown	151 (75.5)	65 (71.4)
Blond or red	49 (24.5)	26 (28.6)
Skin type according to the Fitzpatrick scale, No. (%)[c]		
I	11 (5.5)	5 (5.5)
II	29 (14.5)	15 (16.5)
III	100 (50.0)	43 (47.3)
IV	60 (30.0)	28 (30.8)
Presence of actinic keratoses, No. (%)		
0-5	132 (66.0)	53 (58.2)
>5	68 (34.0)	38 (41.8)

Abbreviations: BCC, basal cell carcinoma; NMSC, nonmelanoma skin cancer; SCC, squamous cell carcinoma.
[a] Follow-up at diagnosis of the first NMSC was measured from transplantation.
[b] Follow-up at diagnosis of the second NMSC was measured from the date of the first NMSC.
[c] Phototype I (scores 0-7): white, very fair; red or blond hair; blue eyes; freckles; always burns, never tans. Phototype II (scores 8-16): white, fair; red or blond hair; blue, hazel, or green eyes; usually burns, tans with difficulty. Phototype III (scores 17-25): cream white, fair; any eye or hair color; very common; sometimes mild burn, gradually tans. Phototype IV (scores 25-30): dark brown; typical Mediterranean Caucasian skin; rarely burns, tans with ease.

Table 3. Risk Factors for Onset of the First NMSC in the Whole Study Cohort of 1934 Patients and of the Second NMSC in 200 Patients With a First NMSC

	First NMSC			Subsequent NMSC			Subsequent BCC			Subsequent SCC		
Risk Factor	Patients, No.	Hazard Ratio[a] (95% CI)	*P* Value	Patients, No.	Hazard Ratio[a] (95% CI)	*P* Value	Hazard Ratio[a] (95% CI)	*P* Value	Hazard Ratio[a] (95% CI)	*P* Value
Sex										
Female	590	1 [Reference]		40	1 [Reference]		1 [Reference]		1 [Reference]	
Male	1344	1.6 (1.2-2.3)	.007	160	1.2 (0.6-2.0)	.60	1.3 (0.5-3.1)	.54	1.6 (0.6-4.1)	.27
Type of transplanted organ										
Heart	458	1 [Reference]		54	1 [Reference]		1 [Reference]		1 [Reference]	
Kidney	1476	0.8 (0.6-1.2)	.49	146	0.9 (0.5-1.5)	.71	0.6 (0.2-1.5)	.32	0.7 (0.2-1.6)	.42
Age at transplantation, y										
<30	370	1 [Reference]		22	1 [Reference]		1 [Reference]		1 [Reference]	
30-50	821	2.2 (1.3-3.5)	.002	84	1.2 (0.5-2.3)	.74	1.2 (0.3-4.4)	.73	0.7 (0.2-2.5)	.67
>50	743	5.4 (3.2-9.0)	<.001	94	1.1 (0.5-2.7)	.68	1.0 (0.2-4.3)	.92	1.2 (0.3-5.0)	.76
Immunosuppressive therapy										
1 Drug + prednisolone	951	1 [Reference]		99	1 [Reference]		1 [Reference]		1 [Reference]	
2 Drugs + prednisolone	983	1.3 (0.9-1.7)	.13	101	0.6 (0.3-1.0)	.09	0.4 (0.2-1.0)	.054	0.7 (0.3-1.4)	.42
Years from transplantation to diagnosis of the first NMSC[b]	NA	NA	NA	NA	0.9 (0.9-1.0)	.89	0.9 (0.9-1.0)	.41	1.0 (0.9-1.0)	.36
Type of the first NMSC										
SCC	NA	NA	NA	109	1 [Reference]		1 [Reference]		1 [Reference]	
BCC	NA	NA	NA	91	0.8 (0.5-1.3)	.61	3.8 (1.6-8.9)	.002	0.2 (0.1-0.4)	<.001

Abbreviations: BCC, basal cell carcinoma; CI, confidence interval; NA, not applicable; NMSC, nonmelanoma skin cancer; SCC, squamous cell carcinoma.
[a] Multivariate estimates were derived using a Cox proportional hazards regression model.
[b] The length of follow-up from transplantation to diagnosis of the first NMSC was inserted in the model as a continuous variable.

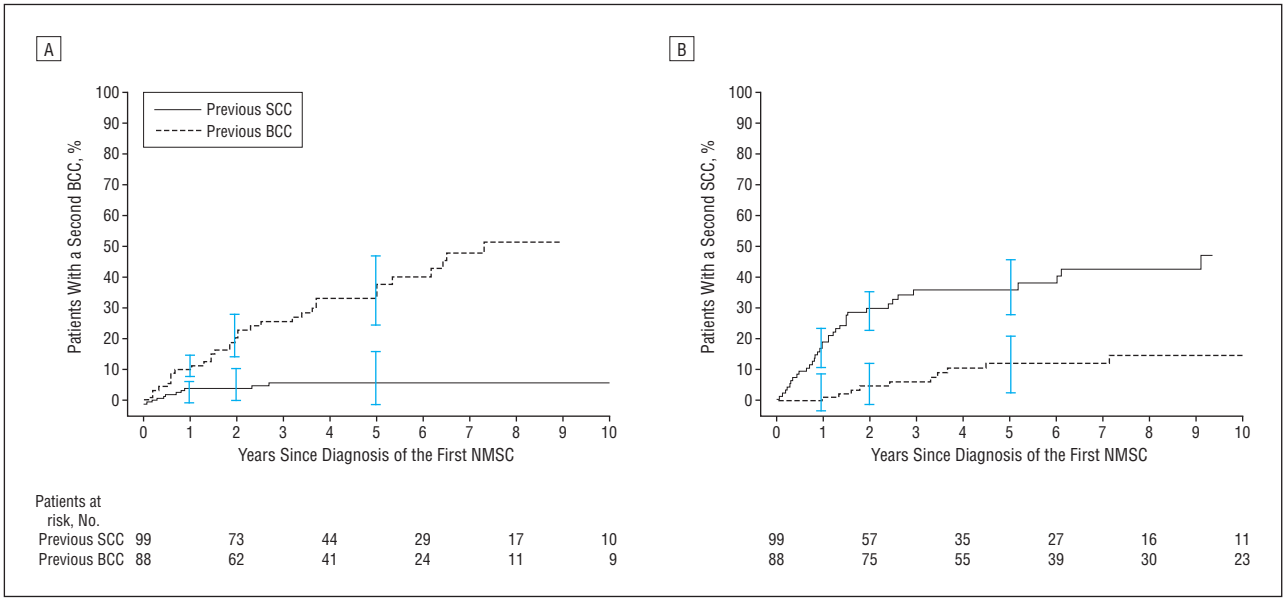

Figure 2. Cumulative incidences of the second basal cell carcinoma (BCC) (A) and of the second squamous cell carcinoma (SCC) (B) in the study population, stratified according to the type of the first nonmelanoma skin cancer (NMSC). Vertical bars indicate 95% confidence intervals.

COMMENT

The main finding of the present study was that transplant recipients with a first NMSC have an increased long-term probability of developing a subsequent NMSC compared with patients with no previous NMSC, thus confirming the findings of Euvrard et al.[16] In the present cohort, the 5-year risk of subsequent NMSC was 41.8%, which is significantly lower than that in the study by Euvrard et al,[16] a difference possibly related to the lower incidence of NMSC in the present study population compared with other studies conducted in northern Europe, Australia, and Canada.[1-8]

None of the clinical risk factors for the first NMSC could predict the onset of the second NMSC, possibly because the risk factors for the first NMSC remain in the patients who develop another. The number of patients with actinic keratoses was higher in patients with and without a subsequent cancer. Only a few of these patients had other risk factors, such as fair skin, blond hair, blue eyes, or multiple skin cancers at the first consultation. Most patients with NMSC belonged to phototypes III and IV, the most common phototypes observed in the nonimmunosuppressed Italian population. Time since transplantation at diagnosis of the first cancer could not predict onset of the subsequent NMSC, supporting the need for regular long-term dermatologic surveillance of all the transplant recipients.

A possible bias in this study was the lack of data about sun exposure (for work and leisure) before and after transplantation and the adoption of sun-protective measures after diagnosis of the first NMSC; however, patients are often not reliable when reporting this information.

The impact of a specific type of immunosuppressive therapy on the onset of skin cancer has been extensively investigated but is still unclear.[2,12,13] In a previous study[4] and in the present data, the risk of NMSC was not related to a specific immunosuppressive regimen. Studying the effect of a single drug protocol may be difficult because the type and amount of immunosuppressive drugs can change during follow-up. Reductions of immunosuppressive therapy, administration of oral retinoids, and conversion to sirolimus-based immunosuppressive therapy have been proposed to reduce the risk of subsequent NMSC in transplant recipients.[21-23] However, at the time of this writing, these protocols were not in use in the transplantation centers of Verona and Bergamo.

In the present cohort, the histologic type of the first NMSC strongly predicted the risk of having a subsequent NMSC of the same type, thus confirming data observed in nonimmunosuppressed patients.[14] This finding may affect the clinical management of patients, especially those with SCC, which may be aggressive and metastatic, as observed in 2 of the present patients. In conclusion, these data demonstrate that solid organ transplant recipients with a first NMSC are at high risk for a second NMSC. No clinical predictors are currently recognized. Intensive lifelong dermatologic follow-up is advisable for these patients.

Accepted for Publication: November 5, 2009.
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Girolomoni. *Statistical analysis:* Tessari, Naldi, Boschiero, and Talamini. *Administrative, technical, and material support*: Nacchia, Fior, Rugiu, Sassi, and Fiocchi. *Study supervision:* Boschiero, Forni, Faggian, Gotti, and Girolomoni.

Financial Disclosure: None reported.

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