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Cytomegalovirus High-risk Kidney Transplant Recipients Show No Difference in Long-term Outcomes Following Preemptive Versus Prophylactic Management

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Background. Following kidney transplantation (KT), cytomegalovirus (CMV) infection remains an important challenge. Both prophylactic and preemptive antiviral protocols are used for CMV high-risk kidney recipients (donor seropositive/recipient seronegative; D+/R–). We performed a nationwide comparison of the 2 strategies in de novo D+/R– KT recipients accessing long-term outcomes. **Methods.** A nationwide retrospective study was conducted from 2007 to 2018, with follow-up until February 1, 2022. All adult D+/R– and R+ KT recipients were included. During the first 4 y, D+/R– recipients were managed preemptively, changing to 6 mo of valganciclovir prophylaxis from 2011. To adjust for the 2 time eras, de novo intermediate-risk (R+) recipients, who received preemptive CMV therapy throughout the study period, served as longitudinal controls for possible confounders. **Results.** A total of 2198 KT recipients (D+/R–, n = 428; R+, n = 1770) were included with a median follow-up of 9.4 (range, 3.1–15.1) y. As expected, a greater proportion experienced a CMV infection in the preemptive era compared with the prophylactic era and with a shorter time from KT to CMV infection ($P < 0.001$). However, there were no differences in long-term outcomes such as patient death (47/146 [32%] versus 57/282 [20%]; $P = 0.3$), graft loss (64/146 [44%] versus 71/282 [25%]; $P = 0.5$), or death censored graft loss (26/146 [18%] versus 26/282 [9%]; $P = 0.9$) in the preemptive versus prophylactic era. Long-term outcomes in R+ recipients showed no signs of sequential era–related bias. **Conclusions.** There were no significant differences in relevant long-term outcomes between preemptive and prophylactic CMV-preventive strategies in D+/R– kidney transplant recipients.

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INTRODUCTION

Cytomegalovirus (CMV) infection and disease are important causes of morbidity and mortality after kidney transplantation.[1-3] With no preventive strategies, approximately 60% of kidney transplant recipients experience active CMV infection, and approximately 20% develop CMV disease.[4] CMV disease after kidney transplantation is nearly 3 times more frequent in CMV-seropositive donor to CMV-seronegative recipient (D+/R–, hereafter called "high-risk") transplantations compared with transplantations with seropositive recipients (R+, hereafter called "intermediate-risk").[4]

In addition to the detrimental effects of posttransplant CMV organ disease, there are several indirect effects of CMV replication that may be associated with a negative impact on long-term graft- and patient survival,[2] including development of biopsy-proven acute rejection[5,6] and diabetes.[7]

In CMV high-risk kidney recipients, both prophylactic and preemptive protocols are recommended as equal preventive strategies, providing adequate CMV DNAemia testing logistics.[8] However, a large head-to-head comparison of the 2 strategies in CMV high-risk kidney transplant recipients has not yet been performed. Current literature on this topic comprises small studies, with <50 CMV high-risk recipients.[8-21] Of those, many are from the era before introduction of low-level calcineurin-based immunosuppression.[22] The available literature indicates similar long-term outcomes despite different clinical patterns during follow-up. In short, prophylaxis leads to fewer and later onset of active CMV infections at the cost of a higher incidence of leucopenia and neutropenia.[9]

The proportion of CMV high-risk solid organ transplant recipients is increasing, and it is projected to continue to increase.[23] The third international consensus guidelines on the management of CMV in solid organ transplantation state that there is a need for more data on preemptive versus prophylactic management of CMV high-risk recipients to establish whether one strategy is superior to the other.[8] To answer the call for data, we have conducted a retrospective nationwide registry-based analysis of long-term outcomes, as well as the frequency of, and time to first active CMV infection in the entire cohort of CMV high-risk and CMV intermediate-risk Norwegian kidney recipients transplanted between 2007 and 2018.

MATERIALS AND METHODS

Study Population

In Norway, all kidney transplantations are centralized at Oslo University Hospital (OUH), Rikshospitalet, with a uniform transplant follow-up protocol for all patients according to risk stratifications, for example, immunological risk and D/R CMV-serological profile. All patients are followed lifelong in the Norwegian Renal Registry (NRR), a consent-based national medical quality registry with >99.9% coverage that collects annual reports of health information.

The present study includes all adult CMV high- and intermediate-risk de novo kidney transplantations in Norway between January 2007 and December 2018 (Figure 1). Of the 3278 kidney transplantations performed in this period, a total of 2198 were included in the analysis. In total, 103 were performed in children <18 y, 222 were synchronous transplantations with other organs, 469 were retransplantations, 5 patients had not consented to register in the NRR, 30 died or experienced graft loss within a week after transplantation, D/R status was lacking in 28 transplantations, and 223 were CMV low-risk (D–/R–). Of the 2198 transplantations included, 749 were performed from 2007 to 2010, whereas preemptive therapy was uniformly used for all patients. Of these, 146 were CMV high-risk and 603 CMV intermediate-risk transplantations. A total of 1449 transplantations were performed between 2011 and 2018, during which time CMV prophylaxis was used for CMV high-risk recipients and the preemptive strategy was continued for intermediate-risk transplantations. In this era, 282 were CMV high-risk and 1167 were CMV intermediate-risk transplantations (Figure 1).

The study was approved by the Regional Ethics Committee of southeast Norway (REK 43147). The informed consent signed by all patients for being included in the registry covered the present study.

CMV-preventive Strategies

From 2007 through 2010, all kidney transplant recipients followed a preemptive CMV strategy. From 2011 CMV high-risk recipients received once-daily valganciclovir prophylaxis (900 mg, dose adjusted according to renal function) for 6 mo. Throughout the entire study period, all patients were subject to at least weekly CMV DNA quantitation during the first 3 mo posttransplant and monthly thereafter up to 1 y posttransplant. **Figure S1** (**SDC**, http://links.lww.com/TP/C748) contains information about the percent of CMV DNA samples taken according to protocol, each week the first 8 wk after transplantation, and thereafter each month up to 1 y. After the first posttransplant year, CMV DNA quantitation was performed on clinical indication.

Treatment with valganciclovir (900 mg twice daily, dose adjusted to renal function) was initiated in case of CMV DNAemia >600 IU/mL plasma (1000 IU/mL plasma from March 2021 at the OUH laboratory because of adjustment in the quantitative method). The length of treatment was at least 3 wk or until 2 negative CMV DNAemia measurements separated by at least 1 wk.

Outcome Measurements

All results of posttransplant CMV DNA quantitation were obtained for the entire study cohort from the 7 laboratories performing this analysis in Norway. Information about mortality, graft loss, acute rejection, and kidney function was obtained from the NRR with a censoring date of February 1, 2022.

The primary endpoint was patient survival among the CMV high-risk kidney transplant recipients in the 2 treatment cohorts. Secondary endpoints included graft loss, death censored graft loss, the combination of death-censored graft loss or doubling of creatinine from baseline (baseline was defined as 8 wk after transplantation), acute rejection, and the proportions of patients with active CMV infection, and time to first CMV infection. Active CMV infection was defined as detection of CMV

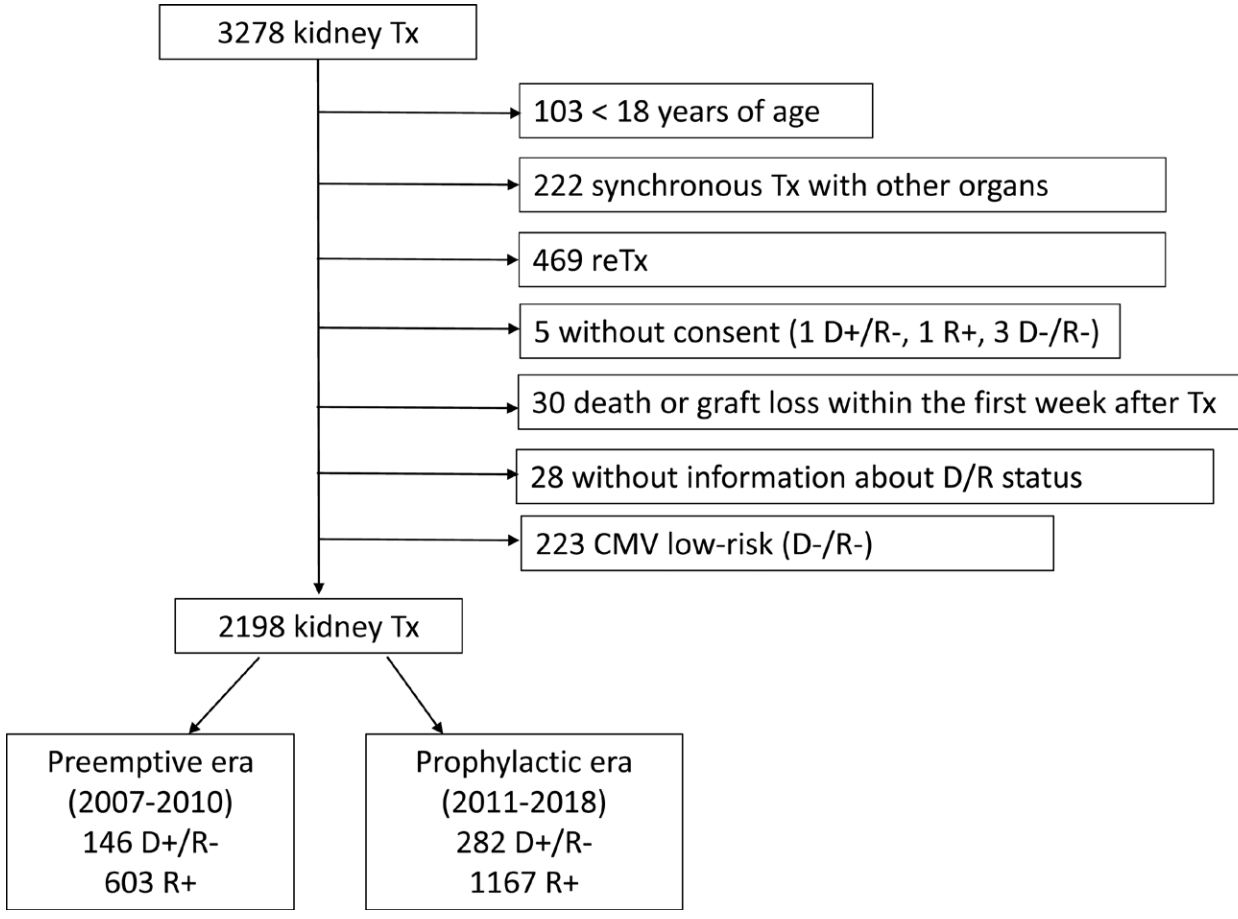

FIGURE 1. Flowchart of the study population from 2007 to 2018. CMV, cytomegalovirus; D+/R–, CMV-seropositive donor to CMV-seronegative recipient; D–/R–, CMV-seronegative donor to CMV-seronegative recipient; D?/R?, unknown CMV serology in donor and/or recipient; R+, CMV-seropositive recipient; Tx, transplantation.

DNAemia ≥600 IU/mL plasma regardless of symptoms. In samples analyzed at OUH after March 3, 2021, the limit was ≥1000 IU/mL plasma because of a change in the quantitative polymerase chain reaction method. High-level CMV activity was defined as CMV DNAemia ≥5000 IU/mL plasma in at least 1 of the positive samples during the respective course of active CMV infection. We only have information regarding CMV infection and not disease.

To exclude potential sequential-era effects, CMV intermediate-risk de novo kidney transplant recipients, managed preemptively during the whole study period, served as a longitudinal control for possible confounding factors that might have impacted any of the primary and secondary endpoints.

CMV DNA Analyses

All 7 laboratories used real-time quantitative polymerase chain reaction analyses for quantitation of CMV DNA. **Table S1** (**SDC**, http://links.lww.com/TP/C748) contains information about the methods used in each laboratory during the study period. One laboratory analyzed CMV DNA in whole blood (<2% of all samples) and all others used plasma. Viral load values are usually $1\log_{10}$ higher in whole blood compared with plasma; however, there is no defined conversion factor.[24] The Norwegian kidney transplant recipients have been treated with the same valganciclovir protocol, regardless of if the CMV DNA analysis was performed in whole blood versus plasma. Therefore, we have not converted the whole blood samples but treated them in the analysis as if they were plasma samples. Results are reported in copies per milliliter or international units per milliliter (**Table S1**, **SDC**, http://links.lww.com/TP/C748). The difference between copies per milliliter and international units per milliliter is not considered significant in the analyses as the conversion factor is 1.1.[25]

All CMV analyses performed during the first 8 wk after transplantation were conducted at the Department of Microbiology at OUH. Also, after this initial phase, most samples (86%) were analyzed at the Department of Microbiology, OUH. On March 3, 2021, the calibration of the analysis at OUH was updated with a World Health Organization standard calibrator (1st World Health Organization International Standard for Human Cytomegalovirus for Nucleic Acid Amplification Techniques, National Institute for Biological Standards and Control code 09/162). This change in calibration resulted in higher viral load numbers. Both before and after recalibration, the analysis was performed within international consensus in comparative quality assurance testing. Before recalibration, the detection limit was 36 IU/mL sample, and the quantitation range was between 200 and 10 000 000 IU/mL. After recalibration, the detection limit is 199 IU/mL sample and the quantitation ranged between 500 and 5 000 000 IU/mL.

Immunosuppressive Protocol

Recipients with standard immunological risk received induction treatment with methylprednisolone and interleukin-2 receptor antibody (basiliximab), and maintenance treatment with glucocorticoids, the cell proliferation inhibitor mycophenolate, and a calcineurin inhibitor (CNI). Target CNI trough concentrations for immunological standard-risk recipients were tacrolimus (Tac) 3 to 7 µg/L (from the year 2016; 4–7 µg/L) from the day of engraftment,[26] whereas for cyclosporine A (CsA), the target was initially 200 to 300 µg/L tapering to 75 to 125 µg/L from 6 mo. At the beginning of the study period, Tac was preferred for younger patients (<50 y), whereas CsA was prescribed to older patients (>50 y) and to patients with body mass index >30 kg/m^2 or with preoperative impaired glucose tolerance. During the study period, the standard regimen was revised, and from January 2011, Tac was preferred for all patients apart from patients with impaired glucose tolerance. Tac was combined with 750 mg mycophenolate mofetil (540 mg mycophenolate sodium) twice daily, whereas CsA was combined with 1000 mg mycophenolate mofetil (720 mg mycophenolate sodium) twice daily. Prednisolone was tapered from 80 mg/d (from the year 2016; 20 mg/d) to 10 mg/d by the second month and further to 5 mg/d from month 6.

Patients classified as immunological intermediate-risk, that is, panel-reactive antibodies (PRAs) >20%, immunological high-risk (known donor-specific antibodies [DSAs] at the time of transplantation), or patients with an ABO blood-type incompatible (ABOi) transplant had higher CNI targets. Tac trough targets were 10 to 12 µg/L for the first month, 6 to 10 µg/L for the second month (ABOi) or the first year (PRA positive/DSA positive), and 5 to 8 µg/L from the third month (ABOi) or after the first year (PRA positive/DSA positive), respectively. Corresponding CsA trough targets were; 250 to 350, 150 to 250, and 100 to 175 µg/L. They also received methylprednisolone in combination with either rituximab, basiliximab, and intravenous human immunoglobulin (ABOi/DSA positive) or ATG (PRA positive) as induction therapy.

Statistical Considerations

Endpoints for the 2 prevention strategies were compared by applying crude Kaplan-Meier survival analyses, the log-rank test, and Cox regression with the "survival" and "survminer" R packages in R (version 4.1.1).[27] Assumptions for the Cox regression (linearity and proportional hazards) were tested with the cox.zph() function in the survival R packages. Results were considered statistically significant when the *P* value was ≤0.05.

RESULTS

Patient demographics are shown in Table 1. The median follow-up time was 9.4 (3.1–15.1) y. During the study period, a total of 203 of 428 patients (47%) in the high-risk group experienced at least 1 episode of active CMV infection, 104 (24%) died, 52 (12%) experienced an isolated graft loss, 71 (17%) had at least 1 acute rejection episode, and 68 (16%) experienced either an isolated graft loss or a doubling of plasma creatinine. In the intermediate-risk group, a total of 458 of 1770 patients (26%) experienced at least 1 episode of active CMV infection, 533 (30%) died, 170 (10%) experienced an isolated graft loss, 257 (15%) had at least 1 acute rejection episode, and 239 (14%) experienced either an isolated graft loss or a doubling of plasma creatinine.

During the study period, a larger proportion of CMV high-risk recipients experienced active CMV infection in the preemptive era compared with the prophylactic era:

TABLE 1.

Demographic data at time of kidney transplantation, categorized by CMV risk (high-risk: D+/R–, intermediate-risk: R+) and CMV-preventive strategy era for high-risk (D+/R–) recipients (preemptive era, 2007–2010; prophylactic era, 2011–2020)

	D+/R–			R+		
Characteristics	2007–2010 Preemptive era (n = 146)	2011–2021 Prophylacitic era (n = 282)	*P*	2007–2010 (n = 603)	2011–2021 (n = 1167)	*P*
Age, y	51.1 ± 15.6	54.3 ± 14.3	0.03	56.7 ± 13.4	57.4 ± 14.2	0.28
Male sex, n (%)	108 (74)	208 (74)	1.00	405 (67)	737 (63)	0.11
BMI, kg/m^2	25.6 ± 4.5	26.3 ± 4.9	0.11	26.1 ± 4.5	26.5 ± 4.7	0.15
Hypertension[a], n (%)	130 (89)	256 (91)	0.37	549 (91)	1051 (90)	0.20
Pretransplant DM, n (%)	18 (12)	53 (19)	0.12	123 (20)	285 (24)	0.06
Living donor, n (%)	48 (33)	63 (22)	0.02	194 (32)	285 (24)	<0.001
Donor age, y	51.1 ± 14.8	53.1 ± 17.4	0.22	51.6 ± 15.4	53.0 ± 17.0	0.09
PRA >20%, n (%)	5 (3)	10 (4)	1.00	33 (5)	50 (4)	0.32
Cold ischemia time, h	10.2 ± 6.8	10.8 ± 6.0	0.36	10.4 ± 6.5	11.1 ± 6.0	0.02
ABOi, n (%)	5 (3)	7 (2)	0.83	8 (1)	34 (2)	0.05
Active smoker, n (%)	24 (16)	50 (18)	0.84	118 (20)	187 (16)	0.07
HLA AB mismatches	2.1 ± 1.1	2.2 ± 1.1	0.21	2.3 ± 1.1	2.3 ± 1.1	0.67
HLA DR mismatches	0.6 ± 0.6	0.8 ± 0.7	<0.001	0.7 ± 0.6	0.9 ± 0.7	<0.0001
Preemptive Tx, n (%)	43 (29)	73 (26)	0.50	152 (25)	303 (26)	0.77
ReTx, n (%)	21 (13)	33 (10)	0.59	124 (17)	228 (16)	0.72

Data are presented as mean ± SD or n (%).

[a]Blood pressure >130/80 mm Hg and/or use of at least 1 antihypertensive drug.

ABOi, ABO incompatible; BMI, body mass index; CMV, cytomegalovirus; D+/R–, donor seropositive/recipient seronegative; DM, diabetes; PRA, panel-reactive antibody; R+, recipient seropositive; ReTx, retransplantation; SD, standard deviation; Tx, transplantation.

93 of 146 (64%) versus 112 of 282 (40%), respectively ($P < 0.001$). Moreover, time to the first CMV infection from time of kidney transplantation was shorter among the high-risk recipients in the preemptive era versus the prophylactic era (Figure 2A; $P < 0.001$). The results showed the same pattern also if a higher DNAemia cutoff was used for definition of CMV infection (CMV DNA ≥5000 IU/mL). Among CMV high-risk recipients, 69 of 146 (47%) in the preemptive era experienced active CMV infection with CMV DNA ≥5000 IU/mL, compared with 84 of 282 (30%) in the prophylactic era ($P < 0.001$; Figure 2B). A sensitivity analysis, excluding whole blood CMV DNA analyses (<2% of all samples), showed the same pattern (data not shown).

In CMV high-risk recipients, there was no significant difference in long-term patient survival between the 2 treatment eras ($P = 0.24$; Figure 2C). Additionally, there was no significant difference in graft loss (Figure 2D), death-censored graft loss, acute rejection episodes, or the combination of death-censored graft loss and doubling of plasma creatinine between the high-risk recipients managed with preemptive versus prophylactic strategies (**Figure S2A–C, SDC**, http://links.lww.com/TP/C748). A sensitivity analysis, excluding patients with a subsequent transplant in the study period, showed comparable results of patient- and graft survival among the high-risk recipients managed with preemptive versus prophylactic strategies (data not shown).

We also investigated if there was a difference in long-term outcomes among patients with a high-level DNAemia cutoff value (≥5000 IU/mL) compared with those with only low-level DNAemia (between 600/1000 and 5000 IU/mL) among CMV high-risk recipients. No significant differences were found (**Figure S3A–E, SDC**, http://links.lww.com/TP/C748).

Multivariate Cox regression models were used for patient death and uncensored graft loss, adjusted for recipient age, sex, and DR mismatch for CMV high-risk recipients. The multivariable Cox regression yielded overall results similar to the Kaplan-Meier analyses (Table 2). Only age was an independent risk factor for patient death and graft loss. Unfortunately, we could not adjust for donor type in the multivariable Cox regression because the hazards for donor type were not proportional. Also, we could not perform a multivariate Cox regression modeling for death-censored graft loss because the hazards for prophylactic versus preemptive therapy were not proportional.

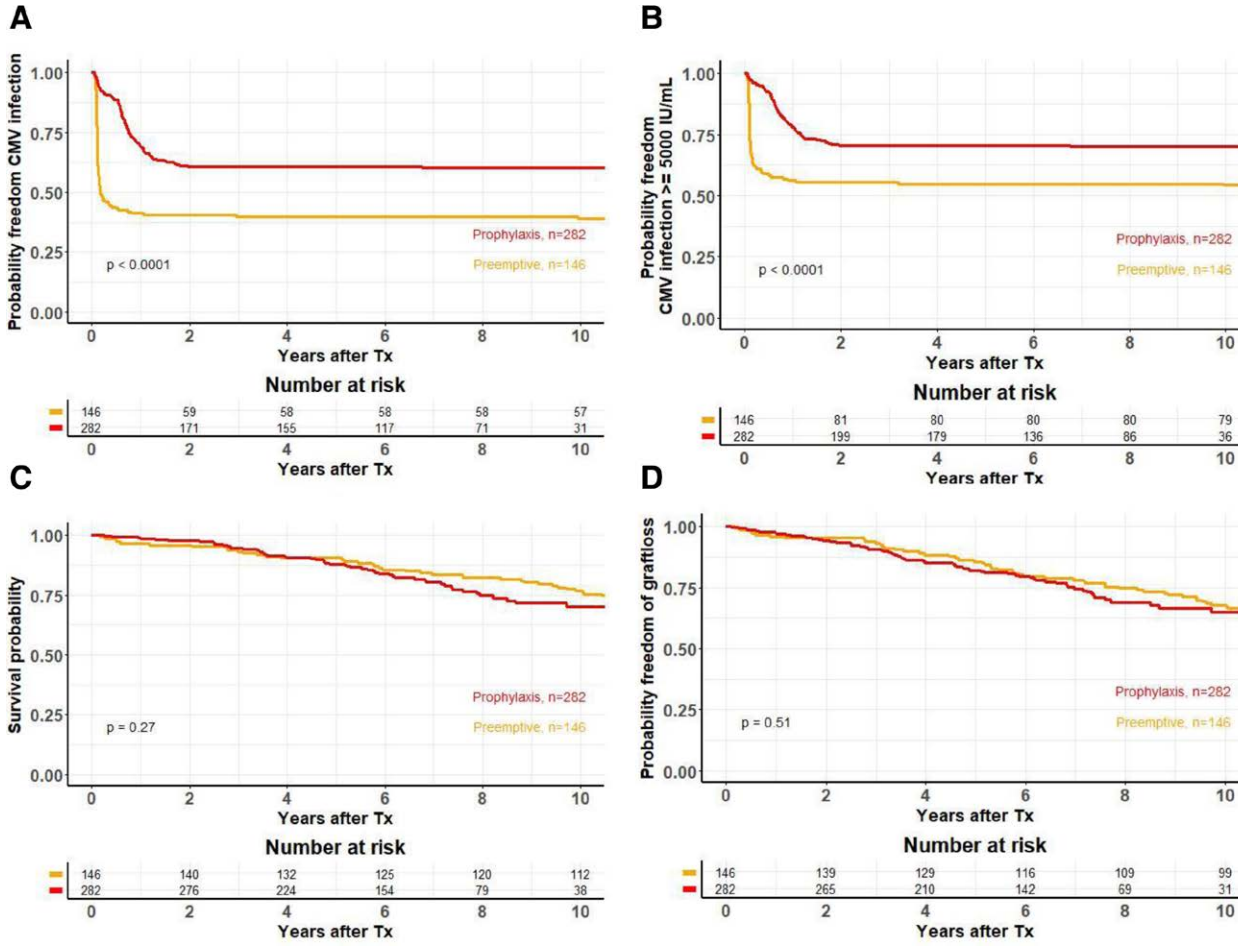

FIGURE 2. Long-term outcomes in D+/R– kidney graft recipients in the 2 eras. A, Occurrence of CMV infection in D+/R– kidney graft recipients by CMV treatment (preemptive or prophylaxis), Norway 2007 to 2021. B, Occurrence of CMV infection ≥5000 IU/mL in D+/R– kidney graft recipients by CMV treatment (preemptive or prophylaxis), Norway 2007 to 2021. C, Patient survival in D+/R– kidney graft recipients by CMV treatment (preemptive or prophylaxis), Norway 2007 to 2021. D, Uncensored graft survival in D+/R– kidney graft recipients by CMV treatment (preemptive or prophylaxis), Norway 2007 to 2021. CMV, cytomegalovirus; D+/R–, CMV-seropositive donor to CMV-seronegative recipient; Tx, transplantation.

TABLE 2.

Results of Cox regression models quantifying the impact of preemptive versus prophylactic treatment on different endpoints

	Cox regression			
	Events	HR	95% CI	*P*
Patient death	104	1.35	0.87-2.09	0.18
Uncensored graft loss	135	1.10	0.75-1.61	0.62

HRs for prophylactic vs preemptive therapy in all D+/R– patients. Adjusted for recipient age, sex, and DR mismatch.
CI, confidence interval; CMV, cytomegalovirus; D+/R–, donor seropositive/recipient seronegative; HR, hazard ratio.

Posttransplant CMV infection and long-term outcomes in CMV intermediate-risk recipients during the 2 time eras (2007–2010 versus 2011–2018) did not show any signs of sequential-era effects. CMV infection incidence and time to infection were similar (Figure 3A), and there was no difference in patient survival, graft loss (Figure 3B and C), death-censored graft loss, acute rejection, or in the combined outcome measure of death-censored graft loss or doubling of creatinine (**Figure S4A–C, SDC**, http://links.lww.com/TP/C748).

DISCUSSION

The results from this large national analysis support the current international guidelines in that long-term outcomes are comparable in CMV high-risk kidney transplant recipients after either preemptive or prophylactic anti-CMV strategies in the early posttransplant phase. This is also the first large analysis on this topic in the era of modern low-level CNI-based immunosuppression.

Until now, most studies have been small, that is, <50 CMV high-risk patients, and have predated the introduction of modern immunosuppressive protocols.[9,10,12,14-17,19-21,28-30] In addition to including a large number of adult kidney transplant recipients, we also had access to *all* CMV DNA measurements performed after transplantation. A total of 58 770 DNAemia measurements were available over a median of 9.4 y. That corresponds to a median of 24 samples per recipient in the 428 CMV high-risk and 1770 CMV intermediate-risk adult kidney transplant recipients. No patient was lost to follow-up.

The results from the present study are consistent with previous findings that show a higher incidence of CMV infection, and shorter time to first CMV infection, in patients managed with a preemptive strategy.[8-18] Overall,

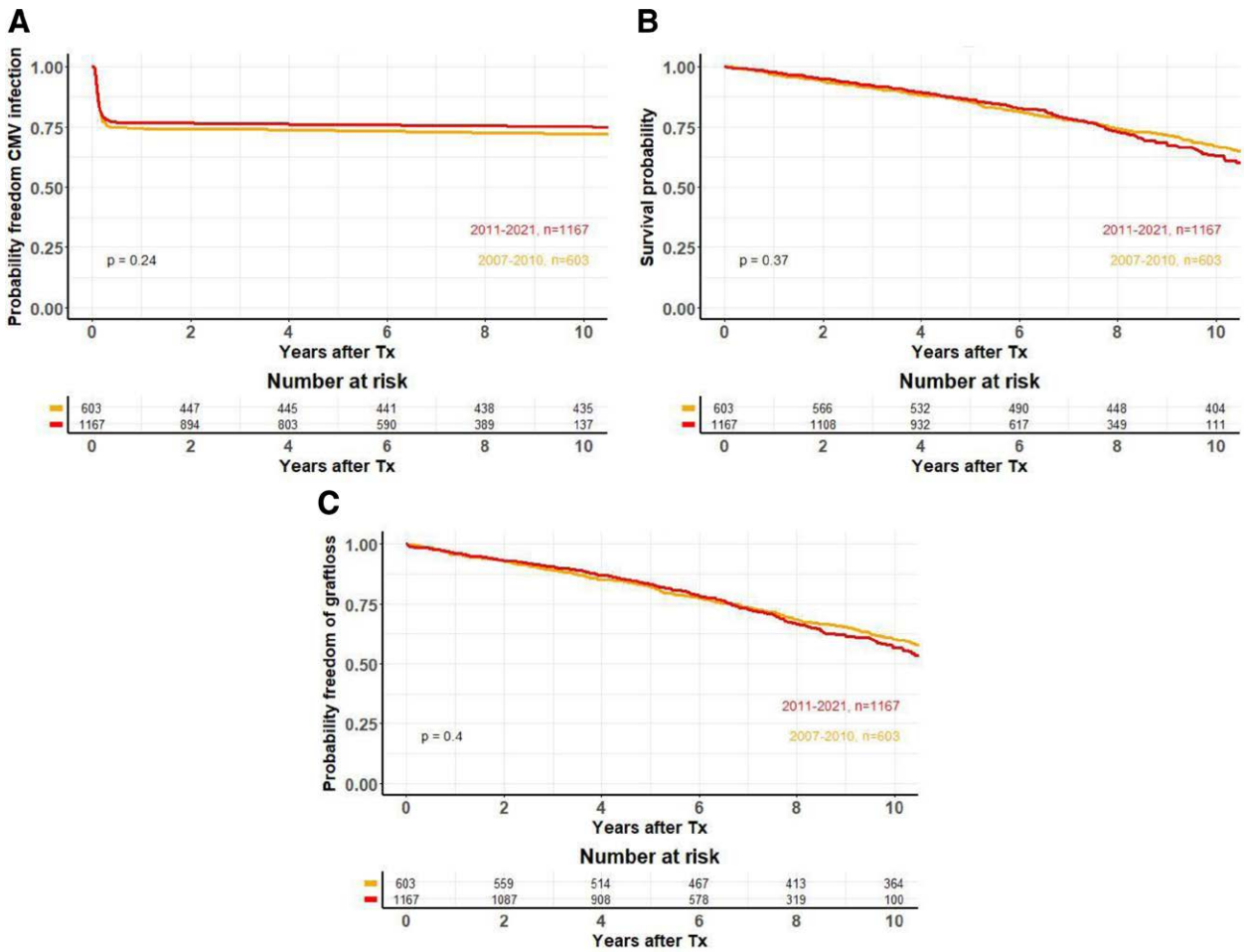

FIGURE 3. Long-term outcomes in R+ kidney graft recipients in the 2 eras. A, Occurrence of CMV infection in R+ kidney graft recipients, by time period, 2007 to 2010 vs 2011 to 2021. B, Patient survival in R+ kidney graft recipients, by time period, 2007 to 2010 vs 2011 to 2021. C, Uncensored graft survival in R+ kidney graft recipients, by time period, 2007 to 2010 vs 2011 to 2021. CMV, cytomegalovirus; R+, CMV-seropositive recipient; Tx, transplantation.

approximately 62% of the recipients on preemptive therapy versus 40% on primary prophylaxis eventually had at least 1 episode of verified active CMV infection after transplantation. This indicates that active CMV infection is prevented rather than only delayed with CMV prophylaxis in CMV high-risk patients.

It is reassuring that the difference in incidence of active CMV infection does not translate into different long-term outcomes, at least when using full-dose valganciclovir therapy and when the laboratory logistics allow for weekly monitoring and rapid communication of the results to the clinician. The current finding of no difference in long-term patient- and graft survival is also in line with most previous publications.[8-20] However, Spinner et al[21] reported a higher incidence of death with a functioning graft in patients subjected to primary prophylaxis, whereas Kliem et al[28] showed improved long-term graft survival with primary prophylaxis. Others have also shown a higher rate of biopsy-proven acute rejection at 1 y in patients on preemptive therapy,[30] although both kidney fibrosis at 3 y and graft survival at 4 y were superior in patients on preemptive therapy.[29]

The main strengths of the present analysis are as follow: the unselected large number of patients included without loss to follow-up and complete availability of all CMV DNAemia measurements. All patients were subjected to the same low-level CNI-based immunosuppressive protocol. The long follow-up time also ensures that the vast majority of CMV infections in this cohort were captured, as shown by the horizontal tail of the Kaplan-Meier curves. However, some transient infection flares after the end of prophylaxis (6 mo posttransplant) may have been missed because of monthly monitoring in this period. Another important limitation is the retrospective and sequential study design that allows for different era effects and confounders to influence the result. Additionally, there is a lack of information regarding individual systemic exposure to ganciclovir in treated patients. Unfortunately, we do not have information about development of CMV disease. The CMV DNA quantitation has been performed by different methods and in different laboratories, although the majority (86%) were analyzed at the transplant center. To some extent, this increases the variability in the quantitative results. However, all the laboratories have participated in quality control programs, helping to ensure a reliable quantitation. Furthermore, the data are robust because they represent real-life results obtained by multiple methods.

One could argue that the sequential change in the CMV-preventive strategy and immunosuppressive protocol during the study period may potentially have affected the risk of active CMV infection and long-term outcomes. However, given that all transplantations were performed at a single national center, applying a centralized protocol at supporting hospitals, this effect will most probably be limited. Also, the comparative analysis of CMV intermediate-risk patients, for whom the CMV-preventive strategy remained unchanged, showed no difference in incidence rates of CMV infection, or long-term outcomes between the 2 periods compared.

In conclusion, our study substantiates previous results from smaller studies, and supports the current international consensus guidelines,[8] that there are no clinically relevant differences in long-term outcomes between CMV preemptive treatment and primary prophylaxis in CMV high-risk kidney transplant recipients. The results are obtained in a setting of appropriate laboratory logistics for CMV DNAemia monitoring and full-dose valganciclovir treatment of detected infections.

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