

ORIGINAL RESEARCH & CONTRIBUTIONS

Temporal Trends in Mortality after Coronary Artery Revascularization in Patients with End-Stage Renal Disease

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<http://dx.doi.org/10.7812/TPP/14-003>**Abstract**

Background: Recent studies that have assessed the comparative effectiveness between coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) in patients with end-stage renal disease (ESRD) that have included analyses of temporal trends in mortality have noted mixed results.

Methods: We conducted an observational longitudinal cohort study of all adults with ESRD undergoing CABG or PCI within Kaiser Permanente Northern California. The primary predictor, index period of revascularization, was categorized into 3 periods: 1996-1999 (reference), 2000-2003, and 2004-2008, with the primary outcome being 3-year all-cause mortality. A multivariable Cox regression model with the assumption of independent censoring was used to determine the adjusted relative risk of the primary predictor.

Results: Among 1015 ESRD patients, 3-year mortality showed no significant change in the 2000-2003 period but was lower during the 2004-2008 period with an adjusted hazard ratio of 0.66 (95% confidence interval: 0.49-0.88; trend test $p = 0.01$). No change in 30-day mortality was noted. Further adjustment for receipt of medications at baseline and after revascularization did not materially affect risk estimates. No significant interactions were observed between the type of revascularization (CABG or PCI) and the period of the index revascularization.

Conclusions: Among a high-risk cohort of patients with ESRD and coronary artery disease within Kaiser Permanente Northern California who were referred for coronary revascularization by either CABG or PCI, the relative risk of mortality in the 2004-2008 period decreased by 34% compared with the 1996-1999 period, with the benefit primarily in the decrease in late mortality.

Introduction

The use of cardiovascular operations and procedures has increased during the past one to two decades.¹ This has been primarily caused by an upsurge in percutaneous coronary intervention (PCI) compared with coronary artery bypass grafting (CABG).² This temporal trend has also been noted in individuals with end-stage renal disease (ESRD).³ Interestingly, accompanying the trend is an established knowledge that there has been a rise in the comorbidity burden in those referred for coronary revascularization procedures.^{4,6} Procedural success^{6,7} and symptom control⁸ have improved

over time with PCI in patients with normal renal function. Similarly, perioperative outcomes have improved with CABG.⁹ However, early and late mortality after coronary revascularization have been consistently higher in patients with ESRD compared with those without kidney disease.¹⁰

Recent studies of the comparative effectiveness of CABG and PCI in patients with ESRD that have included, as part of their main analyses, an assessment of the secular trends in mortality have shown mixed results.^{11,12} To specifically address this knowledge gap, we studied a large community-based sample of patients with

ESRD who underwent coronary revascularization by PCI or CABG to characterize the temporal trends in mortality in the years 1996-2008. We hypothesized that there would not be any significant temporal changes in mortality in the extremely high-risk cohort of ESRD patients after undergoing coronary revascularization.

Methods**Study Population**

Our source population included members of Kaiser Permanente Northern California (KPNC), a large integrated health care delivery system. This study was approved by the KPNC institutional review board. A waiver of informed consent was obtained owing to the nature of the study.

Our target population included adult members receiving chronic dialysis identified from a comprehensive Health Plan ESRD treatment registry who underwent coronary revascularization by either PCI or CABG from January 1, 1996, through December 31, 2008. We identified a coronary revascularization procedure on the basis of procedure codes for CABG or PCI (furnished upon request) without a concomitant valve or other cardiac surgical procedure. Patients were followed-up until death or they were censored when they met any of the following criteria: end of study as of December 31, 2008, organ transplantation, or disenrollment from the Health Plan.

Study Outcomes and Definitions

The primary outcome of the study was all-cause mortality at three years (see statistical analysis section), which was ascertained using Health Plan databases, state death certificates, and Social Security

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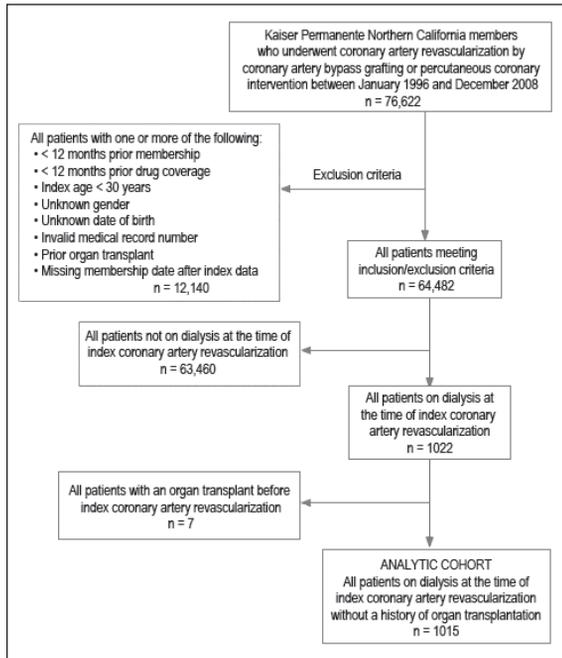


Figure 1. Creation of the study cohort.

Administration files through December 2008, which was the latest available complete vital status data at the time of planned analysis. For analysis purposes, we categorized the primary predictor, index period of coronary revascularization, into three periods: 1996-1999 (reference), 2000-2003, and 2004-2008, because the type of stents being implanted became consistent around the year 2004.

We obtained information from Health Plan clinical and administrative databases on baseline and longitudinal patient demographic characteristics, clinical characteristics, medication exposure, and selected laboratory data using previously described approaches.^{13,14} The baseline clinical variables that were obtained included age at index revascularization, sex, duration of dialysis before index revascularization, and history of tobacco use, myocardial infarction, diabetes mellitus, hyperlipidemia, hypertension, heart failure, liver disease, lung disease, stroke/transient ischemic attack, and atrial fibrillation/flutter (codes available upon request). The baseline and time-varying medications that were obtained included angiotensin-converting enzyme inhibitor (ACE-I), angiotensin receptor blocker (ARB), beta-blockers, calcium-channel blockers, diabetes medi-

cations, and HMG-coenzyme A reductases (statins), on the basis of information from dispensed prescriptions and refill patterns as previously described.¹⁵

Statistical Analysis

An initial bivariate analysis stratified by period was performed using the Fisher exact test or χ^2 analysis for categorical variables and the Kruskal-Wallis rank test for continuous variables. Multivariable Cox regression models were created to estimate the hazard ratios (HRs) (95% confidence intervals [CIs]) for the primary predictor for the outcome 3-year mortality under the assumption of independent censoring.¹⁶ An assessment of the proportionality assumption was

checked by hypothesis testing and by using scaled Schoenfeld residuals against time to determine nonproportionality by graphically assessing for a nonzero slope for each covariate one at a time.¹⁶ No gross departure from the proportionality assumption was noted. We then plotted the survivor function after a fully fitted Cox model. To assess whether baseline medications or time-varying medications affected the summary estimate of the primary outcome, a series of additional extended Cox regression models were conducted that adjusted for baseline and time-varying medications individually and together. All statistical analyses were performed using Stata, version 12 (College Station, TX).

Table 1. Baseline clinical variables stratified into three periods

Variable	1996-1999, n = 176	2000-2003, n = 309	2004-2008, n = 530	p value
Age (%)				
< 65 years	52.8	52.4	51.9	0.86
65-75 years	34.7	33.3	32.3	0.86
> 75 years	12.5	14.3	15.8	0.86
Sex (%)				
Women	30.1	34.9	38.7	0.11
Men	69.9	65.1	61.3	0.11
Duration of dialysis (years \pm SD)	2.3 \pm 2.9	2.4 \pm 2.5	2.4 \pm 2.4	0.19
Baseline comorbidities (%)				
Tobacco use	30.7	46.0	47.9	< 0.001
Myocardial infarction	31.8	40.4	46.6	0.002
Diabetes mellitus	64.8	68.9	79.1	< 0.001
Hyperlipidemia	54.6	82.2	93.8	< 0.001
Hypertension	75.6	93.5	97.4	< 0.001
Liver disease	1.1	3.2	5.5	0.03
Lung disease	13.6	23.0	27.0	0.001
Heart failure	29.6	37.9	42.1	0.012
Stroke/transient ischemic attack	3.4	10.4	6.4	0.01
Atrial fibrillation/flutter	11.4	12.9	16.8	0.13
Number of comorbidities (mean \pm SD)	1.9 \pm 1.2	2.5 \pm 1.3	2.9 \pm 1.2	< 0.001
Baseline medications (%)				
ACE-I	31.3	34.0	31.1	0.67
ARB	5.1	11.6	18.9	< 0.001
Beta-blockers	44.9	61.8	71.5	< 0.001
Diabetes medications	40.3	49.5	59.1	< 0.001
Calcium channel blockers	63.6	57.0	59.6	0.36
Statins	21.0	49.5	66.6	< 0.001
Type of revascularization (%)				
PCI	36.9	53.1	64.2	< 0.001
CABG	63.1	46.9	35.9	< 0.001

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; SD = standard deviation.

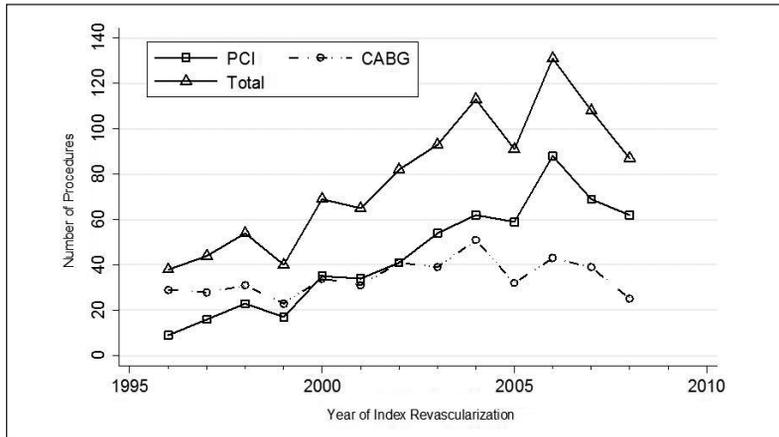


Figure 2. Number of index coronary revascularization procedures (CABG and PCI) in the years 1996-2008.

CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention.

Results

Baseline Characteristics

Figure 1 shows how patients entered into the current study. The characteristics at baseline of the 1015 patients in the cohort are shown in Table 1. The mean age, sex, duration of dialysis, and hemoglobin levels (not shown) were similar across the 3 periods (p = not significant). All comorbidities were significantly more prevalent during the later periods except for atrial fibrillation and stroke/transient ischemic attack. Also, the average number of comorbidities present at the time of coronary revascularization increased significantly by period (p < 0.001). The use of ARBs, beta-blockers, diabetes medications, and statins was higher in the later periods

(p < 0.001) but use of ACE-I (p = 0.67) and calcium channel blockers (p = 0.36) was not. Table 1 and Figure 2 show that the proportion of patients treated with PCI within KPNC has increased over time compared with CABG (p < 0.001). The use of drug-eluting stents understandably has increased over time (p < 0.001). The number of vessels bypassed decreased significantly (p = 0.002), whereas the number of vessels that underwent PCI had a nonsignificant decrease (p = 0.48) during the study period.

Primary Outcome

Table 2 shows early and late survival estimates in the overall as well as in the revascularization-specific groups. The

crude incident rate of death was 256.6 (95% CI = 216.1-304.7) per 1000 person-years for the period 1996-1999; 273.7 (95% CI = 238.2-314.5) per 1000 person-years for the period 2000-2003; and 234.5 (95% CI = 203.2-270.7) per 1000 person-years for the period 2004-2008.

The unadjusted HR for 3-year mortality in the 2000-2003 period was 1.01 (95% CI = 0.77-1.32), whereas in the 2004-2008 period it was 0.84 (95% CI = 0.64-1.09), compared with the reference 1996-1999 period. However, in the full model that was adjusted for age, sex, duration of dialysis, and baseline comorbidities, the HR for mortality in the 2000-2003 time period was 0.85 (95% CI = 0.63-1.14), whereas in the 2004-2008 time period it was significantly decreased at 0.66 (95% CI = 0.49-0.88), compared with the reference period, with a significant trend test of p = 0.01 across the periods. Furthermore, using index revascularization year as a continuous variable, we found that every 1-year increase in the index revascularization year was associated with a 6.0% decrease in the adjusted relative risk of death (p = 0.001). Further adjustment for baseline and/or time-varying medications did not qualitatively change the summary estimate (data not shown).

Timing of Mortality and Interaction with Type of Revascularization

Table 3 notes the adjusted HR for early and late mortality for each individual period compared with the reference period. Early (30-day) mortality after revascularization showed no significant adjusted differences for the periods 2000-2003 and 2004-2008, compared with the reference 1996-1999 period. However, late mortality at 1 year (HR 0.58, 95% CI = 0.39-0.85) and 3 years (HR 0.66, 95% CI = 0.49-0.88) in the 2004-2008 period had a significantly lower adjusted relative rate of death compared with the 1996-1999 period. This was not noted for the time period 2000-2003. Figure 3 is the fitted survival curve stratified by period of index coronary revascularization and demonstrates this improvement in mortality in the latest period. This overall decrease in mortality was seen in both the CABG and PCI subgroups as relatively equal (Figure 4). Furthermore, we specifically did not find

Survival probability	1996-1999, % n = 179	2000-2003, % n = 309	2004-2008, % n = 530
Overall			
30 day	92.6	90.9	93.6
1 year	72.2	73.1	77.9
3 year	47.4	47.1	52.1
PCI			
30 day	95.4	92.1	94.4
1 year	63.3	72.3	77.6
3 year	42.5	44.3	48.8
CABG			
30 day	91.0	89.6	92.1
1 year	77.5	74.0	78.4
3 year	50.3	50.6	57.6

CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention.

Table 3. Adjusted hazard ratio with a 95% CI p value for early (30-day) and late (1-year, 3-year) mortality in the 2000-2003 and 2004-2008 periods compared with the reference period of 1996-1999.^a

Variable	Hazard ratio (95% CI)	p value
30-day mortality		
2000-2003	1.38 (0.67-2.82)	0.38
2004-2008	0.96 (0.46-2.00)	0.90
1-year mortality		
2000-2003	0.84 (0.57-1.25)	0.39
2004-2008	0.58 (0.39-0.85)	0.01
3-year mortality		
2000-2003	0.85 (0.63-1.13)	0.27
2004-2008	0.66 (0.49-0.88)	0.01

^a Model includes the primary predictor categorized year of revascularization adjusted for age, sex, duration of dialysis before revascularization, and baseline comorbidities (tobacco use, myocardial infarction, dyslipidemia, hypertension, heart failure, liver disease, lung disease, atrial fibrillation/flutter, stroke/transient ischemic attack). CI = confidence interval.

any significant interactions between the type of revascularization and the year of index revascularization to our primary outcome.

Number of Baseline Comorbidities

When comorbidity was assessed as a continuous variable in a model adjusted for revascularization year, age, sex, and duration of dialysis, each additional comorbidity was associated with an 11.4% (95% CI = 3.7%-19.7%) increased risk of death.

Discussion

The findings from this study provide further insight and clarification into the temporal trends of mortality in the years 1996-2008 in a known high-risk cohort of patients with ESRD. Although recent studies have noted some mixed results,^{11,12} we believe that the findings from our study are consistent with an optimistic perspective. We found that among a diverse, community-based cohort of adults with ESRD receiving chronic dialysis who underwent coronary revascularization at KPNC, there was a 34% decrease in the adjusted relative risk of 3-year all-cause mortality in patients revascularized in the 2004-2008 period compared with the 1996-1999 period with a significant trend test across all periods, suggesting a graded improvement over the periods. We further noted that this secular trend of improvement in mortality in the 2004-2008 period was limited mainly to late (1- and

3-year) mortality and not early (30-day) mortality. The benefit appeared to be irrespective of the revascularization modality (PCI or CABG) chosen, with no observable interaction between index period of revascularization to revascularization type. Lastly, the presence or absence of medications at baseline or in follow-up during the study period did not explain our findings. Of note, this study did not address the comparative effectiveness between CABG and PCI. Future work from our group will address this further.

There have been 2 recent observational studies that included, as part of their main analyses, data on temporal trends in mortality after coronary revascularization in the ESRD cohort. Chang et al,¹¹ using the US Renal Data System, primarily assessed the differences in

death and myocardial infarction between CABG and PCI in ESRD patients receiving chronic dialysis. Their analysis, which included secular trends in survival at 1, 2, and 5 years after multivessel coronary revascularization, is relevant to the current discussion. They noted crude 1-year survival in 1997 at 71% (95% CI = 69%-74%) similar to that in 2008 of 72% (95% CI = 70%-74%). Two- and 5-year risks similarly showed no significant variation over time, and they noted that "survival rates remained relatively constant over the study period." Shroff et al¹² showed that 2-year survival after CABG in the 2004-2009 period was 60%, which had increased from 56% in the 1995-1998 period. They noted that "survival has improved somewhat in the contemporary era." Our current study noted that crude 30-day survival was not materially different between the periods. However, 1-year survival was 72.2% in the reference period and improved to 77.9% in the 2004-2008 period. Moreover, 3-year survival was 47.4% in the reference period but increased to 52.1% in the 2004-2008 period. Although these values were crude survival probabilities, this corroborated the decreased incidence rate from 273.7 per 1000 person-years in the period 2000-2003 to 234.5 in the 2004-2008 period. As incidence rate incorporates person and time, it is thought to be a better unit for comparison, and this also showed a nonsignificant decrease in mortality.

In comparison with the previous studies mentioned, we expanded our analysis further and addressed the important issue

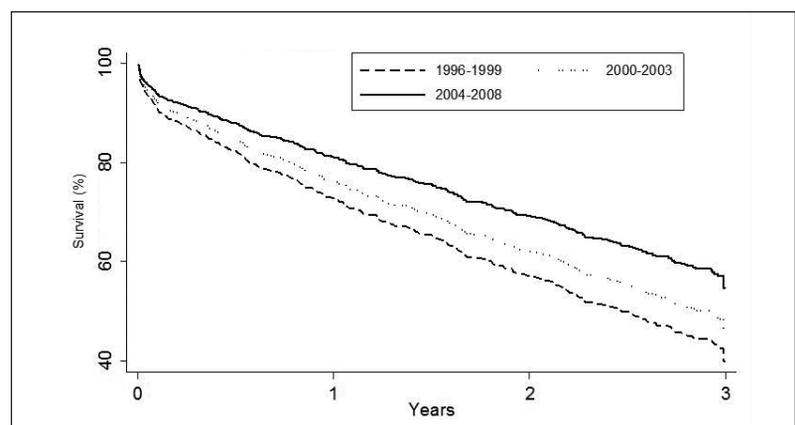


Figure 3. Fitted survival curve stratified by period of index coronary revascularization. Model similar to Table 3.

of confounding by secular changes in baseline comorbidity to obtain a risk ratio. Specifically, there was an increase in all of the examined baseline comorbidities, except for prior stroke or transient ischemic attack and atrial fibrillation, as well as in the average number of comorbidities. This has been well documented in the general population,^{4,6} and our findings of this similar trend existing in patients with ESRD should not be of any surprise even in this high-risk population. In fact, we noted that for each 1-unit increase in baseline comorbidities there was an independent 11.4% increased risk of death. Therefore, to appropriately account for the confounding of baseline comorbidities over time and to obtain the direct effect of the index period of coronary revascularization, we appropriately adjusted for this case-mix in baseline comorbidities to obtain what we feel is an accurate estimate of the effect size of the association of the index period of coronary revascularization to mortality.

The use of cardioprotective medications in our cohort differed from previous studies. In comparison with a study of hospitalized ESRD patients presenting with an acute myocardial infarction,¹⁷ the use of cardioprotective medications in our study was much higher; beta-blocker use in the later years was 71.5% (vs 37.7%), and the use of ACE-I and ARB in our study was close to 50% (vs 27.6%). However, when comparing medication usage with patients who have preserved renal function, use of ACE-I, beta-blockers, and statins was higher.⁸ In our study, which focused only on patients with ESRD, the variation in use of these agents could be reflective of physician knowledge of the varying benefit: risk ratio (variations in dialysis clearance, nonpressor effects, and anaphylactoid dialyzer reactions) in medications such as ACE-I or ARB¹⁸ or of no presumed benefit with the use of statins.¹⁹ Although we noted an improvement in mortality, the mechanism of this improvement is not fully understood and was beyond the scope of the present study. Whether this improvement was because of changes in dialysis techniques,²⁰ increased use of implantable cardiac defibrillator,²¹ improvements in PCI or CABG technology, or other mechanisms is presently unknown. There was an increase in the use

of cardioprotective medications at baseline over time, possibly correlating with the associated increased comorbidities as well as the more aggressive population-based prevention efforts at KPNC during the period,¹³ but adjusting for baseline and time-varying medication use did not change the summary estimate. Of note, we were not able to appropriately capture aspirin use in all patients because many patients obtain it over the counter.

Finally, our finding of lower mortality in the most recent period for patients with ESRD undergoing revascularization appears to be congruous with the overall 28.4% decrease amongst all dialysis patients noted in the 2012 US Renal Data System.²² Although our cohort would probably be considered a “sicker” cohort, we believe the finding from this study allows room for optimism in the setting of a disease with an arduous future. The Healthy People program was an initiative set forth by the US Department of Health and Human Services initially in 1979 and updated most recently for “Healthy People 2020.”²³ The goal is to reduce the total death rate for patients on dialysis to 190.8 deaths per 1000 patient-years by the year 2020 from a rate of 192.5 in 2010 (an understandably small decrease in this high-risk cohort). Achieving a similar difference for the subset of ESRD patients receiving coronary revascularization will be an even bigger challenge because they represent an even higher risk category among those on ESRD. Their incidence of death in our study for the 2004-2008 period was 234.5 per 1000 person-years, and the more aggressive use of pharmacologic therapies for secondary prevention in later years did not appear to explain the improved outcomes. Our findings strongly support the need to develop and to test novel interventions for ESRD patients who continue to be underrepresented in clinical trials.²⁴

Strengths and Limitations

Our study had several strengths. A primary strength is the inclusion of a community-based cohort of ESRD patients whose clinical characteristics and longitudinal care were comprehensively captured through electronic medical records and other complementary databases. Ascertainment of the primary outcome relied on multiple sources and previously validated

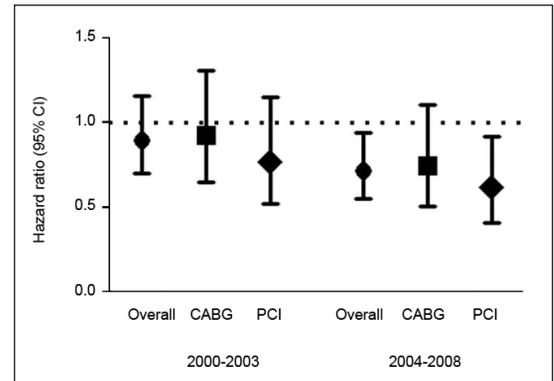


Figure 4. Adjusted mortality in the overall, CABG, and PCI cohort stratified by period of revascularization compared with the reference period 1996-1999. Model similar to Table 3.

CABG = coronary artery bypass grafting; CI = confidence interval; PCI = percutaneous coronary intervention.

methods.¹³ Unlike typical claims data, our data set included important clinical and treatment information to provide a more detailed characterization of this study sample. We were also uniquely positioned to assess how differential use of medications over time may have affected the observed outcomes. The limitations of this study are those that are inherent in all observational studies. Specifically, to truly assess secular trends one would need to obtain a large set of covariates that includes angiographic, physician, and hospital characteristics as well as incorporating all the changes in technology of PCI and CABG and also details on the specific indications for referral for revascularization. These were beyond the scope of the current study. Although not a true weakness, our findings may not be fully generalizable to other ESRD populations or practice settings, although it is known that the KPNC population is highly representative of the local surrounding and statewide population except for slightly lower representation at the extremes of age and income.²⁵

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In summary, in patients with ESRD receiving coronary revascularization by either PCI or CABG, there was a decrease in all-cause mortality with the advantage

primarily in late mortality during the period 1996-2008. Additional research is needed to identify which interventions can improve the outcomes in this high-risk patient population. ♦

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