Impact on cardiovascular risk follow-up from a shift to the CKD-EPI formula for eGFR reporting: a cross sectional population-based primary care study.

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-003631
Article Type:	Research
Date Submitted by the Author:	20-Jul-2013
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Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Cardiovascular medicine, Renal medicine
Keywords:	PRIMARY CARE, Chronic renal failure < NEPHROLOGY, Coronary heart disease < CARDIOLOGY, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Ischaemic heart disease < CARDIOLOGY

Title: Impact on cardiovascular risk follow-up from a shift to the CKD-EPI formula for eGFR reporting: a cross sectional population-based primary care study.

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Word count: 2814 words.

Keywords: Chronic Kidney Disease, primary health care, glomerular filtration rate, cardiovascular risk management

Abstract

Objective: To assess the impact on cardiovascular risk factor management in primary care by the introduction of CKD-EPI for eGFR reporting.

Design and setting: Cross-sectional study of routine healthcare provision in 47 primary care practices in the Netherlands with MDRD eGFR reporting.

Methods: eGFR values were recalculated using CKD-EPI in patients with available creatinine tests. Patients reclassified from CKD stage 3a to CKD stage 2 eGFR range were compared to those who remained in stage 3a for differences in demographic variables, blood pressure, co-morbidity, medication usage and laboratory results.

Results: Among the 60,673 adult patients (37% of adult population) with creatinine values, applying the CKD-EPI equation resulted in a 16% net reduction in patients with CKD stage 3 or worse. Patients reclassified from stage 3a to 2 had lower systolic blood pressure (139.7 vs 143.3 mmHg $p<0.0001$), higher diastolic blood pressure (81.5 vs 78.4 mmHg $p<0.0001$) and higher cholesterol (5.4 vs 5.1 mmol/l $p<0.0001$) compared to those who remained in stage 3a. 463 (32%) of those reclassified out of a CKD diagnosis had no co-morbidities that would qualify for annual CVD risk factor assessment and 20 (12% of those with sufficient data) had a EuroSCORE CVD risk > 20% within ten years.

Conclusion: Use of the CKD-EPI equation will result in many patients being removed from CKD registers and the associated follow up. Current risk factor assessment in this group may be lacking from routine data and some of the reclassified group are at increased risk for cardiovascular events.

ARTICLE SYNOPSIS

Article Focus

- Chronic kidney disease is common and increases the risk of cardiovascular events, as well as progression to end stage renal failure.
- Estimated GFR alone can determine diagnosis of chronic kidney disease for many patients with implications for monitoring and assessment of cardiovascular risk.
- The MDRD equation is used in many countries to estimate GFR but the CKD-EPI equation is more accurate and may be adopted, although its impact on reclassification of CKD in primary care is unknown.

Key Messages

- Patients reclassified out of a CKD diagnosis are younger, more likely to be female with lower prevalence of co-morbidities
- Compared with patients who are not reclassified and remain in stage 3a CKD, patients reclassified to stage 2 range eGFR have lower systolic blood pressure, but higher diastolic blood pressure and higher cholesterol.
- 32% of patients reclassified to stage 2 range eGFR have no other co-morbidities that would flag them as requiring cardiovascular risk assessment in primary care, yet 12% of these patients have elevated cardiovascular risk.

Strengths and Limitations

- A large population based study using routinely collected healthcare data with generalizable results.
- CKD categories were based on one eGFR measurement
- Not all patients reclassified out of CKD had data available for cardiovascular risk assessment and the extent of missed high risk patients with CKD-EPI may be under-estimated.

Introduction

Chronic Kidney Disease (CKD) is common and causes substantial morbidity, mortality and healthcare expenditure because it is associated with an increased risk of cardiovascular events as well as progression to end stage renal failure.(1-3) Estimated GFRs are routinely calculated from measured serum creatinine values to assess renal function.(4) The eGFR is central to the classification of CKD into different stages and is used alongside other evidence of kidney disease, such as structural abnormalities on imaging or albuminuria. A key consequence of this staging of CKD is that it is used to guide the management of cardiovascular risk markers, the frequency of follow up and the need for referral(4) and in the Netherlands there is guidance for primary care on how to assess and manage cardiovascular risk.(5)

Globally, the standard equation used by healthcare laboratories to calculate eGFR is the four variable Modification of Diet and Renal Disease Study (MDRD) equation.(6) Using pooled data from diagnostic accuracy studies, a newer more accurate equation was developed – the Chronic Kidney Disease Epidemiological Collaboration (CKD-EPI) equation.(7-10) Several studies have shown that use of the CKD-EPI equation to calculate eGFR leads to a reduction in CKD diagnoses in younger patients, but an increase in CKD diagnoses in elderly patients.(11, 12) Data from cohort studies and US health insurance schemes have shown that CKD stage derived from the CKD-EPI formula better predicts cardiovascular events and so cardiovascular risk than does CKD stage derived from the MDRD equation.(13-15)

The impact on cardiovascular risk follow-up and management in primary care arising from the introduction of the CKD-EPI formula for routine eGFR reporting has not been assessed. We do know that the CKD-EPI formula will change the CKD stage of many patients.(11) This has important implications as current guideline-driven care pathways emphasise different intensities of monitoring and drug prescribing according to CKD stage. For patients who have their CKD diagnosis removed entirely (by a shift from an MDRD-derived eGFR of <60 to a CKD-EPI-derived eGFR of >60 ml/min/1.73m^2 in the absence of known albuminuria or other evidence of kidney disease) this will lead to less intensive treatment of cardiovascular risk factors unless there are co-morbid diagnoses such as diabetes mellitus that necessitate enrolment in a cardiovascular risk management programme.

In the Netherlands, all routine chronic disease management is undertaken by primary care physicians in community based practices, and national guidance on monitoring is available.(4) Reporting of eGFR with serum creatinine in the Netherlands began in 2006 and the EuroSCORE model for cardiovascular risk assessment is currently recommended for use in primary care.(5) The aim of the study was to determine the cardiovascular risk profile of patients who no longer fulfilled CKD stage 3 criteria when using the CKD-EPI formula for eGFR reporting.

Method

Recruitment of patients

This study used patient data from general practices that participated in a cluster randomised controlled trial on the effect of web-consultation between a general practitioner (GP) and nephrologist on face to face referrals - the CONTACT study (Consultation Of Nephrology by Telenephrology Allows optimal Chronic kidney disease Treatment in primary care, Netherlands Trial Registration code 2368). The CONTACT study recruited practices during a CKD management course for GPs in the eastern Netherlands. Forty seven non-academic general practices participated and in the current study the latest data was analysed from their registered populations' electronic medical records between 01-01-2008 and 30-06-2011.

Estimation of renal function

Estimated GFRs were calculated for patients aged 18 years or older using both the MDRD and CKD-EPI equations.(6, 7) The most recent serum creatinine values were selected and were either standardised to isotope dilution mass spectrometry (IDMS) or subject to the appropriate correction factor for laboratories using the Jaffé technique.(16)

Patient characteristics

Demographic and clinical data including age, sex, albuminuria, co-morbidities, medication, blood pressure and lipid levels were extracted from electronic medical records (Table 3). Albuminuria was divided into microalbuminuria and macroalbuminuria. Microalbuminuria was defined as a urinary albumin to creatinine ratio (ACR) of 2.5–25 mg/mmol in men and 3.5–35 mg/mmol in women. Higher ratios were considered to reflect macroalbuminuria. If the ACR was not available we used a urine albumin concentration >20–200 mg/l for microalbuminuria and >200 mg/l for macroalbuminuria.(17) Co-morbidities were classified using the International Classification of Primary Care (ICPC) codes as a history of the following diseases: cardiovascular disease (K74-K77, K89, K90, K92), diabetes mellitus (T90) and hypertension (K86, K87). Anatomical Therapeutic Chemical (ATC) codes were used to select prescriptions from 2010, and included angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (C09), diuretics (C03) and statins (C10). Blood pressure was reported as the mean of the two most recent measurements. In order to reduce potential under ascertainment bias for chronic disease, if patients were prescribed medications for chronic disease management without an appropriate code e.g. antihypertensive medication without hypertension coded in the medical record, we assumed that the relevant chronic disease was present, even if not coded.

Analysis

The prevalence of CKD stages derived from use of the MDRD and CKD-EPI equations were calculated using the size of the registered population aged 18 years and over as the denominator. Demographic and clinical features of patients reclassified from CKD stage 3a to stage 2 by using the CKD-EPI equation were compared with patients who remained in stage 3a. Next, we specifically described characteristics and cardiovascular risk profile of patients whose CKD stage 3a was changed to stage 2 who had no diagnosed co-morbidity that would otherwise have necessitated their participation in a cardiovascular risk management programme. To assess cardiovascular risk profile we applied the EuroSCORE 10 year risk for cardiovascular disease.(5) To ensure conservative estimation we assumed negative smoking status when lacking. Continuous data were compared using t-tests and categorical data were analysed using chi square tests. Analysis was conducted using SPSS version 20.0 (IBM PASW statistics 20).

Ethical approval

Ethical approval was given for the CONTACT study by the accredited Medical Research Ethics Committee Arnhem/Nijmegen registration number 2010/187.

Results

Practice population

The 47 study practices serve a population of 207,469 people of whom 162,562 were over 18 years of age. Between 2008 and 2011, 37% of all adults registered with these practices (n = 60,673) had their serum creatinine measured. In the over 65 age group this figure rose to 71% (20,959 out of 29,591).

Study population

The use of the CKD-EPI equation changed the CKD stage for 20% of patients (n = 12,278) with a measured serum creatinine value. This reclassification resulted in a 16% net reduction in the total number of individuals with CKD stage 3 or worse: 1428 patients were reclassified from stage 3a to stage 2, whereas 195 patients were reclassified from stage 2 to stage 3a (Table 1). As a consequence the prevalence of detected CKD stages 3 – 5 declined from 4.8% to 4.0% in the total adult population.

eGFR categories with MDRD (ml/min/1.73m2)	eGFR categories with CKD-EPI (ml/min/1.73m2)						Total
	>90	60 - 89	45 - 59	30 - 44	15 - 29	<15	
>90	15195	741	0	0	0	0	15936
60 – 89	9580	27184	195	0	0	0	36959
45 – 59	0	1428	4338	146	0	0	5912
30 – 44	0	0	106	1345	63	0	1514
15 – 29	0	0	0	9	290	7	306
<15	0	0	0	0	3	43	46
Total	24775	29353	4639	1500	356	50	60673

Table 1: Reclassification of primary care patients when using CKD-EPI instead of MDRD.

Thirty-two per cent (*n* = 19,235) of those who had a serum creatinine measurement also had a urine assessment to evaluate albuminuria, and the numbers of patients with different levels of albuminuria are shown in Table 2, stratified by eGFR category using both MDRD and CKD-EPI eGFRs. Overall in those tested, the prevalence of microalbuminuria was 12.1% (n=2322) and of macroalbuminuria was 1% (n=284) Of the patients reclassified from CKD stage 3a to stage 2 eGFR range, albuminuria was tested for in 43% (n=617) and the prevalence of microalbuminuria was 8.6% (n=53) and of macroalbuminuria was 1.5% (n=9).

		eGFR categories (ml/min/1.73m2)					
		>90	60 - 89	45 - 59	30 - 44	15 - 29	<15
MDRD eGFR	Macroalbuminuria	37	97	67	55	21	7
	Microalbuminuria	437	1140	489	219	35	2
	No albuminuria	3016	10768	2297	496	51	1
CKD-EPI eGFR	Macroalbuminuria	43	98	61	53	21	8
	Microalbuminuria	516	1089	442	226	47	2
	No albuminuria	4678	9617	1783	490	58	3

Table 2: Numbers of patients with proteinuria according to estimated eGFR category with either MDRD or CKD-EPI in 19235 primary care patients with available results of urine analysis.

Patients reclassified out of CKD compared to patients remaining in stage 3a

Compared to patients whose CKD stage remained 3a, those who were reclassified to stage 2 range eGFR using the CKD-EPI equation were younger, more were female, with less microalbuminuria, a comparable prevalence of macroalbuminuria, fewer co-morbidities and were prescribed fewer anti-hypertensive and lipid-lowering drugs (Table 3). Systolic blood pressure was significantly lower and diastolic blood pressure significantly higher in patients reclassified out of CKD. Total cholesterol and LDL-cholesterol were significantly higher in this group.

Variable	**Remained in stage 3a (N=4338)**	**N of available data**	**Reclassified out of CKD (N=1428)**	**N of available data**	**P for comparison**
Age	74.0 (9.5)	4338	60.3 (9.5)	1428	<0.0001
Female	61% N=2654	4338	76% N=1087	1428	<0.0001
Cardiovascular disease	36% N=1566	4338	18% N=250	1428	<0.0001
Hypertension	57% N=2463	4338	47% N=666	1428	<0.0001
Diabetes	26% N=1134	4338	17% N=243	1428	<0.0001
None (also excluding albuminuria)	21% N=924	4338	39% N=557	1428	<0.0001
Statins	46% N=2000	4338	33% N=475	1428	<0.0001
ACE inhibitors and/or Angiotensin II receptor antagonists	54% N=2349	4338	37% N=533	1428	<0.0001
Diuretics	43% N=1862	4338	26% N=367	1428	<0.0001
Creatinine in µmol/l	102 (14.3)	4338	93 (11.4)	1428	<0.0001
Chol/HDL ratio	4.2 (1.4)	3338	4.3 (1.6)	1118	0.020
Total cholesterol in mmol/l	5.1 (1.2)	3498	5.4 (1.1)	1157	<0.0001

HDL in mmol/l	1.31 (0.40)	3454	1.36 (0.41)	1150	<0.0001
LDL in mmol/l	3.05 (1.02)	3451	3.31 (1.01)	1150	<0.0001
Triglycerides in mmol/l	1.65 (0.83)	3458	1.64 (1.05)	1156	0.616
Albumin/creatinine ratio†	1.0 (0.9 – 2.5)	2092	0.9 (0.7 – 1.2)	583	<0.0001
Albumin urine in mg/l†	6.0 (2.9 – 17.0)	1174	3.0 (2.0 – 8.0)	348	<0.0001
Microalbuminuria	410	2161	53	617	<0.0001
Macroalbuminuria	55	2161	6	617	0.113
Diastolic blood pressure in mm Hg	78.4 (9.4)	3540	81.5 (9.0)	1043	<0.0001
Systolic blood pressure in mm Hg	143.3 (17.5)	3540	139.7 (15.8)	1042	<0.0001

Table 3. Characteristics of patients reclassified out of CKD compared to those who remained in stage 3a. Values are mean (standard deviation) or †median (1^{st}, 3^{rd} quartile). Percentages of prevalence are calculated with the denominator of available data

Patients reclassified out of CKD without other diagnosed co-morbidities

463 patients (32% of those reclassified out of CKD) would be removed from a cardiovascular risk management programme as they were not diagnosed with other co-morbidities (Table 4). Cholesterol measurement was performed in 64% of patients. The majority of patients had not had an albuminuria assessment. Blood pressure was measured in 218 patients and 111 (51%) of them had elevated values ≥ 140/90 mmHg requiring further monitoring. Similarly, 20 out of 172 patients (12%) with sufficient data to complete cardiovascular risk assessment had a EuroSCORE 10 year cardiovascular disease risk of >20%.

	Mean (SD)	No of patients with available data
Age	56.6 (10.0)	463
Female	79%	463
Creatinine in µmol/l	97 (11.9)	463

Chol/HDL ratio	4.4 (1.6)	285
Total cholesterol in mmol/l	5.8 (1.0)	295
HDL in mmol/l	1.44 (0.43)	290
LDL in mmol/l	3.78 (0.89)	289
Triglycerides in mmol/l	1.42 (0.76)	289
Albumin/creatinine ratio	0.9 (0.5-0.9)	65
Albumin urine in mg/l	2.9 (2.0-5.25)	38
Diastolic blood pressure in mmHg	81.8 (9.1)	218
Systolic blood pressure in mmHg	138.0 (16.7)	218
Either systolic or diastolic blood pressure ≥ 140/90 mmHg	111	218
EuroSCORE 10 year cardiovascular disease risk ≥ 20%	20	172

Table 4: Characteristics of patients reclassified out of CKD without diagnosed co-morbidity.

Patients reclassified into a CKD diagnosis

195 patients were reclassified from stage 2 to stage 3a CKD, and of these, 166 (85%) had existing co-morbidities that would already have identified them for cardiovascular risk assessment. Among the 29 patients who had no identifiable co-morbidity, their mean age was 85.4 years (SD 5.1, youngest 76 years) and in the 11 patients with recorded BP, mean values were 137.5 mmHg (SD 13.7) /71.4 mmHg (5.4). Of the eight patients with sufficient data for CVD risk scoring, six patients were > 20%, although all were outside the age range for accurate scoring and may qualify for high risk status on age alone.

Discussion

Principal findings

Application of the CKD-EPI equation to our study population resulted in a net 16% decrease (prevalence from 4.8% to 4.0%) in the total number of individuals with CKD stage 3 or worse based on eGFR criteria. Patients reclassified from stage 3a to stage 2 were younger, more were female with lower prevalence of co-morbidities and a differential effect was seen on blood pressure with lower systolic but higher diastolic mean values. Although 32% of patients reclassified out of stage 3a had no documented co-morbidity that would entail annual cardiovascular disease (CVD) risk factor assessment as part of a chronic disease management programme, an estimated 12% of these patients did indeed have elevated CVD risk. Not all reclassified patients had an adequate CVD risk factor assessment so our results may underestimate the scale of this problem, although it is still likely that CKD-EPI reclassification has reduced the number of low risk patients in stage 3.

Differences in prevalence of prescribed lipid lowering therapy may explain why higher total cholesterol and LDL levels were seen in patients who were reclassified to a higher eGFR value, above the 60 ml/min/1,73m^2 cut off. More frequent co-morbidities, in patients in CKD stage 3 using CKD – EPI estimation, are indications for improved risk factor control for primary and secondary prevention are likely to explain the greater statin prescribing and lower lipid levels in patients retaining a stage 3 CKD diagnosis. However, the differences in blood pressure are not explained by differences in antihypertensive prescribing, due to the differential effect on systolic and diastolic blood pressure.

Strengths and limitations

One of the strengths of our study is the use of routine general practice data from a large population which enhances the generalisability of our results. In the absence of a screening programme, existing CKD diagnoses are made from clinician-directed testing and so cannot provide true population prevalence. However, we were able to include a large proportion of the (potential) CKD population as creatinine results were known in 71% of patients over 65 years of age. A strength of the analysis of patients reclassified from stage 3 CKD to stage 2 eGFR range, is that we made the conservative assumption that patients prescribed medication used to treat co-morbidities did indeed have that co-morbidity, even if it was not coded in the medical record. This will have the effect of reducing the number of patients in the sub group without co-morbidity reclassified out of a CKD diagnosis, and the impact that we did find is likely to under-estimate the effect of re-classification. Furthermore, our study accurately reflects the changes in CKD stage and status that will arise from use of the CKP-EPI formula in current clinical practice with clinician-directed testing.

A limitation of this study is that our classification of patients was based on a single creatinine result, whereas guidelines recommend two measurements ≥ 3 months apart before making a diagnosis. However, this is unlikely to affect the proportional changes seen to a great extent given the size of our dataset and is in line with the approach used in most CKD studies.(11, 12, 18-20) Albuminuria and cardiovascular risk factor assessment was incomplete and this highlights an area for quality improvement in general practice. However, despite the low usage of albuminuria assessment, our estimates of the gains and losses in CKD diagnoses are likely to be reliable. We did not have ethnicity data and assumed our population to be Caucasian. This assumption was based on ethnicity data from the Statistics Netherlands that shows 92% of the population is Caucasian in the eastern Netherlands.(21) Both MDRD and CKD-EPI equations estimate true GFR and are therefore prone to some degree of error.

Comparison with existing literature

In other studies, a similar decrease in CKD prevalence was found; from 4.2% to 3.9% and 4.9% to 4.4% in two large adult UK population-based studies,(18) and from 5.41% to 4.80% in the Quality Improvement in CKD trial.(22) Also, CKD stage alteration in one fifth of all patients with a creatinine measurement by use of the CKD-EPI equation is a figure consistent with previous estimates.(11)

Cohort studies stratifying patients at baseline with reclassified CKD stages using CKD-EPI eGFRs report lower cardiovascular events in these patient groups during follow up,(13-15) suggesting that overall, risk prediction is improved. Two studies that analysed the characteristics of patients re-classified out of a CKD diagnosis using CKD EPI are in agreement with our results, finding that these patients were predominantly women, of younger age, and with less diabetes compared to those whose CKD stage remained unchanged.(19, 23) White et al. did not report diastolic blood pressure or LDL-cholesterol levels, but found that those reclassified out of CKD had lower systolic blood pressure, similar total cholesterol levels and lower triglycerides levels and a lower 10 year CVD risk.(19) Although we also found lower systolic blood pressure levels, we found higher total (and LDL) cholesterol and no reduction in triglyceride levels. The differential effect on systolic and diastolic blood pressure may be explained by the fact that the reclassified patients in our study had a younger mean age. Diastolic blood pressure has been shown to be high in early middle age and then fall in older age as systolic blood pressure increases.(24) Patients with a CKD-EPI eGFR sufficiently higher than their MDRD eGFR to lose their CKD diagnosis are young enough to exhibit this effect.

Korhonen et al. found no significant differences in cardiovascular risk factors between those reclassified and those remaining in the same CKD stage when the CKD-EPI formula was used, but the study size (n=1747)was probably too small to detect the differences we identified.(20) No previous study has examined medication use.

Meaning of the study

Introduction of CKD-EPI to calculate eGFR can be expected to lower primary care workload and reduce treatment and costs in patients who overall have low cardiovascular risk. Whilst the CKD-EPI equation shows greater calibration than the MDRD equation in that it more accurately stratifies patients in terms of their cardiovascular risk, we have found that by using routinely collected data in primary care, patients reclassified out of CKD had a more favourable cardiovascular profile in terms of age and co-morbidity compared to patients who remained in stage 3a. However, there is a small group of patients with elevated cardiovascular risk who will no longer be detected and managed.

Unanswered questions and future research

Uncertainty remains about the impact on patient cardiovascular follow-up in those who lose their CKD diagnosis with use of the CKD-EPI formula. Although fewer cardiovascular events are seen in patients reclassified from retrospective observational data, (13-15) their care would have been guided by MDRD staging rather than the less severe CKD stage seen with CKD-EPI. Prospective follow up studies are therefore required to appropriately determine the impact of CKD-EPI GFR estimation on cardiovascular events.

Current guidelines apply a fixed eGFR threshold to define CKD with the result that some patients will not be diagnosed with CKD in the presence of reduced renal function for their age group. This effect may be particularly relevant in younger patients, who may for example have an ‘normal’ eGFR of 80 ml/min/1.73m2 which is ‘normal’ according to Dutch guidelines(4) yet it is be significantly lower than the average GFR in people of a similar age.(25) It may be more appropriate to report the statistical deviation of eGFR values from age-matched population means and to highlight those that lie below a given percentile for further assessment and cardiovascular risk assessment. The CKD-EPI equation would make such an approach more feasible since it can be used to accurately report on eGFR > 60 ml/min/1.73m2.(8) Further research is therefore needed to determine the feasibility of age matched eGFR reporting to guide patient management.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf. JFMW received research grants from Amgen, Genzyme and Pfizer for the Masterplan study. None of the other authors had financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Funding: The Dutch Kidney Foundation funded the study (Nierstichting Nederland). The Department of Primary and Community Care received a non-conditional grant from Amgen. DSL and CAO’C are supported by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre

Programme. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Additional information

This study was performed according to the Code of Conduct for Health Research which has been approved by the Data Protection Authorities for conformity with the applicable Dutch privacy legislation.

Contribution: DSL, CAO'C, NSdH conceived the study. All authors contributed to study design. VvG and DSL undertook the analyses. All authors contributed to data interpretation. VvG and DSL drafted the manuscript and all authors contributed to revisions and approved the final version.

Data sharing: No additional data available.

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