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Cardiovascular Disease in Chronic Kidney Disease: Leading Cause of Mortality

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Target Audience & Learning Objectives

This CME activity is intended for nephrologists, primary care physicians, and healthcare practitioners who treat patients with CKD.

Upon completing this CME-certified monograph, you should be able to:

1. Identify the risk factors that contribute to CVD and mortality in CKD patients.
2. Understand the consequences of vascular calcification and loss of elasticity and how these factors lead to CVD and mortality in CKD patients.
3. Discuss how the proper management of secondary hyperparathyroidism (SHPT) in CKD improves mineral metabolism, vascular elasticity, and inflammation that contribute to enhanced cardiovascular risk in these patients.
4 Review therapeutic measures that reduce cardiovascular risk factors in CKD patients and lead to improved survival outcomes.

Instructions

The participant should read the learning objectives and review the activity in its entirety. After reviewing the material, the participant should complete the Activity Self-assessment Test consisting of a series of multiple-choice questions.

Upon successfully completing this activity as designed and achieving a passing score of 70% or higher on the Activity Self-assessment Test, participants will receive a continuing education credit letter awarding the appropriate credit and the Activity Self-assessment Test answers four to six weeks after the receipt of the registration and evaluation materials.

Estimated time to complete this CME-certified monograph as designed is .5 hours.

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This activity was reviewed for relevance, accuracy of content, balance of presentation, and time required for participation by Mark A. Gendreau, MD, MS; Alexandra Mangili, MD, MPH; and Paula Brathwaite, MD.

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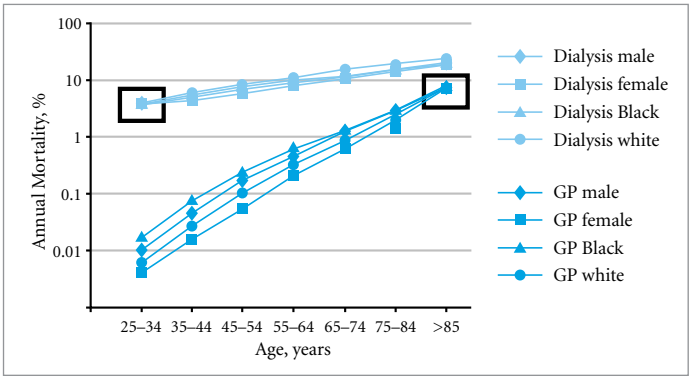
Cardiovascular disease (CVD) and its complications are the leading cause of death in patients on dialysis, with more than 40% of dialysis patients dying of cardiovascular diseases.[1] Coronary risk is magnified in chronic kidney disease (CKD) and end-stage renal disease (ESRD) patients[2] with estimated cardiovascular mortality approximately 10-20 times greater in ESRD patients than in the general population.[3] The HOPE study reported that early renal insufficiency is an independent predictor of cardiovascular outcomes.[4] The results of a large community-based population study demonstrated an independent, graded association between the risk of death, cardiovascular events, and hospitalization and estimated GFR.[5] The National Kidney Foundation and the American Heart Association now recognize CKD as an independent cardiovascular risk factor.[6,7] Recent data indicate that CKD is a predictor of myocardial infarction and death, independent of other clinical variables[8,9,10] and that the risk of death increases substantially with the progression of CKD.[5,11] The exact biological mechanisms by which CKD is related to CVD remains unknown, but most likely include numerous traditional risk factors such as hypertension, diabetes, and hyperlipidemia, as well as risk factors associated with CKD that include vascular calcification, vitamin D deficiency, and secondary hyperparathyroidism.[12]

This Nephrology Express Report examines the associations between CKD and cardiovascular disease, and reviews data recently presented at a symposium in May 2008 in Washington, DC, entitled *Cardiovascular Disease in CKD: Strategies for Minimizing Mortality*. Cardiovascular disease associated with CKD is the result of interplay among multiple factors. In this regard, there has been increasing attention on the disorders of calcium and phosphorus metabolism and abnormal bone turnover and its treatment, which result in medial calcification and may contribute to the excess cardiovascular morbidity and mortality observed in CKD. Further, accumulating evidence indicates that vitamin D therapy reduces mortality in CKD patients. An overview of evidence relating CKD and CVD, the possible mechanisms involving arterial calcification, and active vitamin D therapy will be discussed. For your benefit, CME questions are included at the end of the monograph.

Prevalence of CVD in CKD

The incidence of CKD in the United States occurs in "one of every nine Americans" according to Sudhir V. Shah, MD, FACP and Director of the Division of Nephrology at the University of Arkansas. Mortality from cardiovascular disease is disproportionately high in patients with ESRD compared to the general population (Figure 1). The evidence that CKD and adverse CHD outcomes are independently associated comes from many community-based studies. In a population-based study using data from the Second National Health and Nutrition Examination Survey (NHANES II) and the NHANES II Mortality Study, investigators examined the risk of death and cardiovascular disease in patients with decreased renal function.[13] Approximately 6453 patients were followed

Figure 1. Cardiovascular mortality in the general population (GP) and in dialysis patients. [adapted from 3]



during a 12 to 16 year period after determination of baseline GFR was determined. Mortality rates and relative hazards of death from all causes, cardiovascular disease, and coronary disease were significantly higher for study subjects with an estimated GFR of < 70 mL/min when compared to the patients with an estimated GFR of (90 mL/min [1.51 (1.19 to 1.91), 1.68 (1.33 to 2.13), and 1.68 (1.23 to 2.30) respectively].

Over 1 million patients with mild to moderate CKD in a California healthcare system were stratified according to GFR.5 The study showed that as GFR decreased, the risk of death, cardiovascular events, and hospitalization increased (Table 1). Over 138,000 cardiovascular events occurred in the group during the follow-up period. The adjusted hazard ratios for cardiovascular events, as compared with patients with an estimated GFR of > 60 mL/min per 1.73 m2, was 1.4, 2.0, 2.8, and 3.4 for patients with an estimated GFR of 45-59 mL/min per 1.73 m2, 30-44 mL/min per 1.73 m2, 15-29 mL/min per 1.73 m2, and < 15 mL/min per 1.73 m2, respectively. The 95 percent confidence intervals for these hazard ratios were all significant. Similar results were found for the risk of death and hospitalization.

The association of CKD with adverse cardiovascular events has prompted investigations into the biological mechanisms that may be responsible for this linkage. One observation is CKD patients with low serum albumin demonstrate a higher risk of mortality. Dr. Shah presented data that shows significant increases in risk of heart disease, heart failure, and mortality with

Table 1. Adjusted Hazard Ratio for Death from any Cause, Cardiovascular events, and Hospitalization of 1,120,295 Patients Stratified according to GFR. † Serves as the reference group. [adapted from 5]

Estimated GFR	Death from Any Cause	Any Cardiovascular Event	Any Hospitalization
	Adjusted hazard ratio (95 percent confidence interval)		
≥60 mL/min/1.73 m²†	1.00	1.00	1.00
45–59 mL/min/1.73 m²	1.2 (1.1–1.2)	1.4 (1.4–1.5)	1.1 (1.1–1.1)
30–44 mL/min/1.73 m²	1.8 (1.7–1.9)	2.0 (1.9–2.1)	1.5 (1.5–1.5)
15–29 mL/min/1.73 m²	3.2 (3.1–3.4)	2.8 (2.6–2.9)	2.1 (2.0–2.2)
<15 mL/min/1.73 m²	5.9 (5.4–6.5)	3.4 (3.1–3.8)	3.1 (3.0–3.3)

Table 2. Association between Mean Serum Albumin and Clinical Outcomes (expressed as the effect of 1 g/dL decrease) in Hemodialysis Patients (n = 261). [adapted from 14]

Outcome	Risk	*P*-Value
Ischemic heart disease		
De novo	5.29	0.001
Recurrent	4.24	0.005
Cardiac failure		
De novo	2.22	0.001
Recurrent	3.84	0.003
Mortality		
All cause	4.33	< 0.001
Cardiac	5.60	0.001
Non-cardiac	3.58	< 0.001

decreases in albumin levels (Table 2).[14] The link between low serum albumin and CHD and increased mortality, may in part be due to inflammation. This is evidenced by the concomitant rise in C-reactive protein observed in these patients. Dr. Shah suggested that elevated urea levels in CKD patients may also relate to increased rates of atherosclerosis due to carbamylation of LDL-cholesterol.

Clinical Implications of Coronary and Vascular Calcification

Peter A. McCullough, MD, MPH, FACC, Clinical Professor, Oakland University School of Allied Health Sciences, William Beaumont Hospital, Royal Oak MI, hypothesized that coronary and vascular calcification may be factors that contribute to increased mortality in CKD patients. Dr. McCullough presented data examining the role of Mönckeberg's sclerosis and atherosclerosis and provided evidence that arterial calcification which occurs in CKD patients, otherwise known as Mönckeberg's sclerosis,[15] involves both the media and the internal elastic lamina of arteries.[16] This process is likely to account for the decreases in pulse wave velocity observed in CKD patients. Dr. McCullough proposed that the coronary artery calcium score (CAC) may be used as a surrogate marker for atherosclerotic burden and that the presence and extent of vascular calcifications were strong predictors of cardiovascular and all-cause mortality in CKD patients (Figure 2).[17]

Kramer et al examined the theory that patients with worsening CKD exhibit higher CAC scores.18 In a cohort of 2961 patients using logistic regression, the association between CAC and stage of CKD was determined (Figure 3). Compared to patients without CKD, patients with stage 3 to 5 CKD were significantly more likely to have CAC scores > 400 (odds ratio 8.35; 95% confidence interval, 1.94 to 35.95). However, after excluding patients with diabetes, the association was markedly reduced. When analyzing the group of patients with CKD stage 3 to 5 and diabetes, compared to subjects with diabetes and no CKD, the CKD patients were nine times more likely to have CAC scores > 10 versus (10 (95% CI, 1.16 to 70.05). The authors concluded that higher CAC scores are likely to be associated with CKD stages 3 to 5, especially in patients with diabetes.

The theory that progressive vascular calcification (VC) is associated with arterial stiffening and increased mortality in patients with stages 4 and 5 CKD was examined in a study by Sigrist et al.[19] The goal of this study was to evaluate if multiple factors contribute to the development and worsening of VC in CKD patients, as well as examining the association between VC and mortality. Vascular calcification was assessed using CT scanning of the superficial femoral artery to generate a calcification score (CaSc) and pulse wave velocity was measured in all participants (n= 101) at baseline, 12, and 24 months.

Figure 2. Increased Calcification Associated with Decreased Survival in Stage 5 CKD Patients. [adapted from 17]

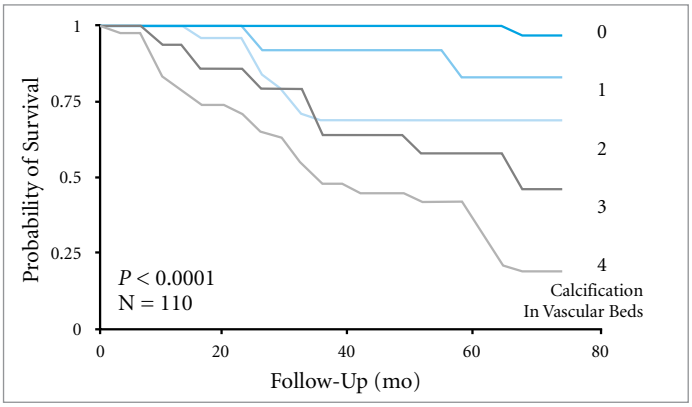
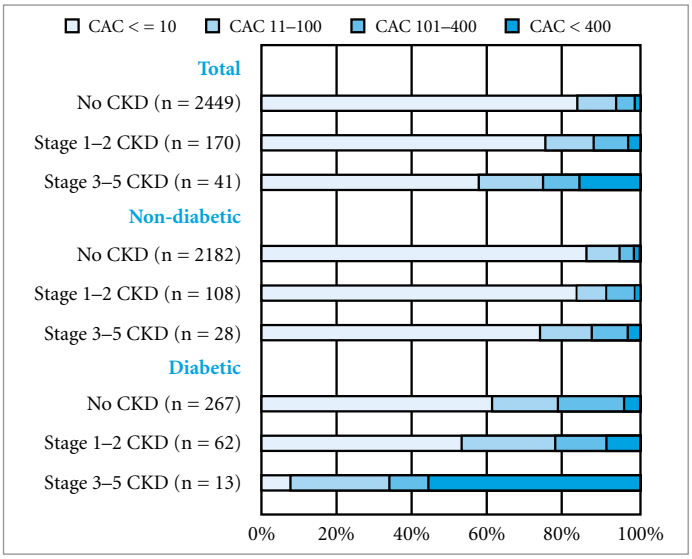


Figure 3. Prevalence of increased coronary artery calcification (CAC) scores by presence of CKD and diabetes in the Dallas Heart Study Population. [adapted from 18]



Over 24 months, CaSc increased in 58 of 101 patients ($P < 0.0001$), with patients undergoing hemodialysis exhibiting the greatest degree of progression. They demonstrated that the change in CaSc correlated significantly with increased arterial stiffening at 12 and 24 months (r = 0.52, $P < 0.001$ and r = 0.33, $P = 0.003$, respectively). They also showed that the change in CaSc was correlated with pulse pressure (r = 0.216, $P < 0.05$) and pulse wave velocity at 24 months (r = 0.329, $P < 0.05$). Forty percent of patients in the study died of cardiovascular-related diseases, and the factors associated with reduced survival included change in CaSc, calcium intake, and low baseline albumin levels. The authors concluded that in patients with stage 4 and 5 CKD, progressive vascular calcification is associated with increased arterial stiffness, and progressive vascular calcification over 12 months was a predictor of death in CKD patients. Although the biologic explanation for the association of CKD and CVD is incomplete, the investigators suggest that progressive arterial stiffening associated with vascular calcification may increase left ventricular afterload and decrease coronary artery perfusion during diastole. Based on these findings, the authors recommend preventing the progression of VC in CKD patients.

Active Vitamin D Therapy to Reduce Cardiovascular Risk and Mortality

Recognizing that prevention of secondary hyperparathyroidism (SHPT) is a key factor in the prevention of coronary and vascular calcification, Myles Wolf, MD, MMSc, Assistant Professor of Medicine at Harvard

Figure 4. Distribution of 25-hydroxyvitamin D levels among 825 hemodialysis patients. The vertical dashed line indicates the lower limit of the normal range for 25-hydroxyvitamin D, 30 ng/mL. [adapted from 20]

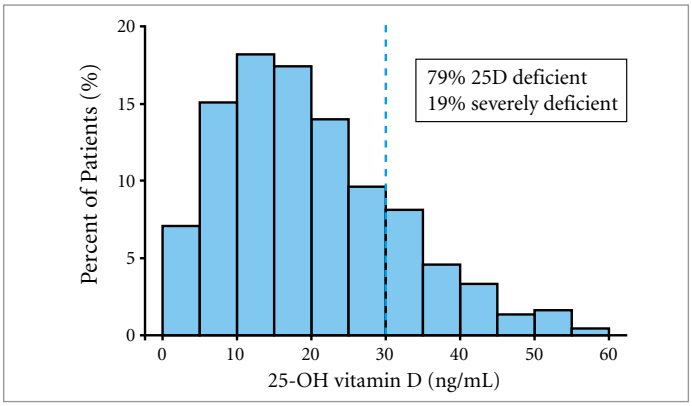
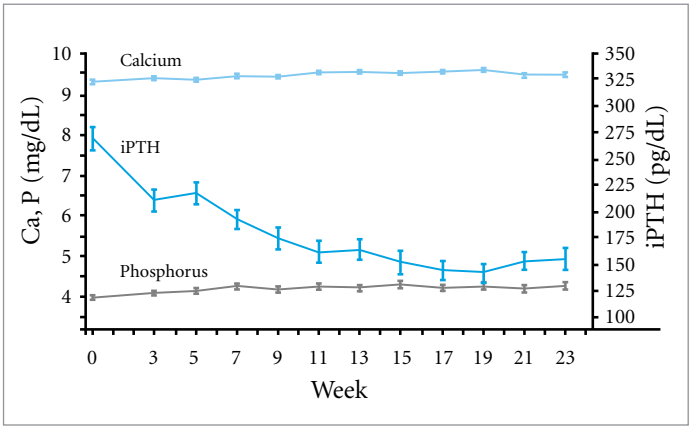


Figure 6. Serum calcium, phosphorus, and PTH levels in CKD patients treated with paricalcitol. [adapted from 22]



Medical School, presented evidence for the role of active vitamin D therapy in CKD. Dr. Wolf is the principal investigator of the ArMORR study, which examined vitamin D levels and mortality in hemodialysis patients.[20] Using a nested case-control analysis, the investigators selected 825 consecutive patients from a cohort of incident hemodialysis patients in the United States. Baseline vitamin D, calcium, phosphorus, and parathyroid hormone levels were measured and the cohort was followed prospectively for 90 days. Seventy nine percent of the patients were deficient in 25-hydroxyvitamin D at baseline (Figure 4).

Low levels of 25-hydroxyvitamin D were associated with increased mortality; however, a significant relationship was discovered between vitamin D levels, treatment with active vitamin D, and survival. Patients with untreated vitamin D deficiency were found to be at a significantly increased risk of mortality compared to patients who had received therapy with active vitamin D (Figure 5).

To investigate the theory that vitamin D treatment is beneficial in preventing death in patients with CKD, Kovesdy et al. performed a retrospective cohort study of 520 male patients with stage 3-5 CKD not receiving dialysis.[21] The primary outcome measure was all-cause mortality as a function of treatment status with activated vitamin D (calcitriol in this study). Secondary outcome measures were progression to ESRD and the composite of predialysis all-cause mortality and ESRD. Approximately 258 patients (49.6%) received calcitriol treatment at baseline. The calcitriol treatment group tended to be older, with lower diastolic blood pressure, higher serum PTH levels, lower GFR, and increased levels of serum phosphorus; all factors that are associated with increased mortality in dialysis patients.

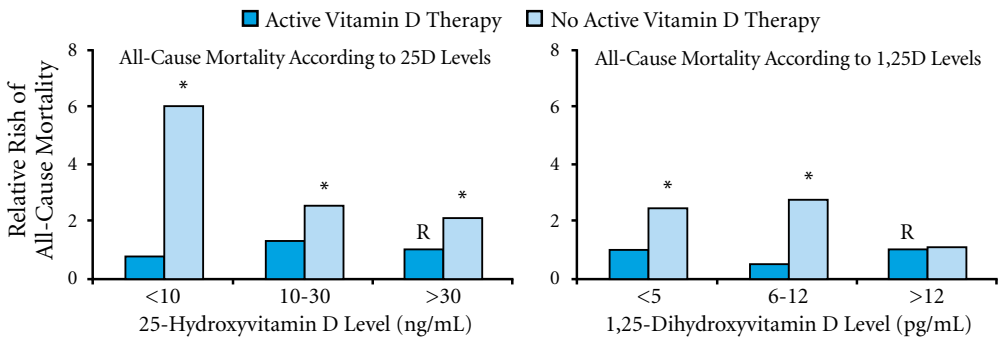
Patients receiving calcitriol had significantly lower rates of mortality ($P < 0.001$) and the incidence rate ratio of death in patients who were treated with calcitriol compared with patients not receiving vitamin D therapy was 0.35 (95% CI, 0.23-0.54; $P < 0.001$). The incidence rate ratio for the combined death and ESRD outcome was 0.46 (95% CI, 0.35-0.61) in adjusted models. The significantly decreased rates of death and ESRD/death were observed for the group that had multiple factors that should have worsened their prognosis. Although the exact mechanism of action for activated vitamin D treatment leading to increased survival is unknown, the investigators postulated that it might be due to effects on proteins and cytokines involved in arterial calcification and plaque formation and preventing clot formation. Because this was an observational study, causality could not be proven, but the authors indicate that randomized clinical trials are warranted to investigate further the link between activated vitamin D and improved survival in patients with CKD.[21]

Dr. Wolf stressed that early screening for elevated PTH levels and vitamin D deficiency in CKD patients is of utmost importance to prevent altered mineral metabolism and increased cardiovascular risk. He encouraged clinicians to "screen earlier" in patients in initial stages of CKD and pointed out that treatment for vitamin D deficiency is essential. There are three FDA approved active vitamin D compounds available; however, Dr. Wolf indicated that compared with calcitriol, the vitamin D analog paricalcitol reduces PTH levels without significant effects on serum calcium and phosphorus levels (Figure 6).[22]

Conclusions

CKD patients have a greater risk of death from cardiovascular causes. Accumulating evidence indicates that vitamin D plays a role in survival of CKD patients; however, further studies are required to examine the association between deficiency and replenishment of vitamin D, SHPT, and cardiovascular disease in CKD patients. Studies examining the role of inflammation, vascular calcification, and therapies that reduce cardiovascular risk in CKD patients are needed. Historically, patients with CKD have been excluded from prospective clinical trials of patients with cardiovascular disease. In a 2006 survey of literature examining coronary artery disease trials, the investigators reported that 75 percent of these trials excluded CKD patients and few studies reported baseline renal function.[23] Clearly, there is a need to examine vitamin D treatment to reduce cardiovascular risk in CKD patients, and future studies will elucidate both the classical and non-classical mechanisms of vitamin D action in CKD management.

Figure 5. All-cause mortality according to 25-hydroxy- and 1,25-dihydroxyvitamin D levels in hemodialysis patients receiving active vitamin D therapy compared with those receiving no active vitamin D therapy. [adapted from 20]



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Activity Self-assessment Test

1. What percentage of dialysis patients die of cardiovascular diseases?
   A. 25%
   B. 40%
   C. 55%
   D. 60%

2. Patients with CKD and low serum albumin:
   A. Have decreased rates of mortality.
   B. Have fewer cardiovascular events.
   C. Have better blood pressure measurements.
   D. Have significantly increased risk of heart disease, heart failure, and mortality.

3. True or false: coronary artery calcium score may be used as a surrogate marker for atherosclerotic burden.
   A. True
   B. False

4. The ArMORR study by Wolf et al. demonstrated that:
   A. Patients who received vitamin D therapy while on dialysis had significantly increased rates of survival compared to untreated vitamin D deficient patients.
   B. Patients who had low vitamin D levels had increased mortality.
   C. Vitamin D treatment had no effect on survival.
   D. A and B are correct.

5. Paricalcitol is an active vitamin D analog which:
   A. Decreases PTH without raising serum calcium and phosphorus levels.
   B. Is not available in the United States.
   C. Is not well tolerated by patients.
   D. Needs additional hydroxylation to be effective.

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1. A B C D
2. A B C D
3. A B
4. A B C D
5. A B C D

I certify that I have completed the activity, "Cardiovascular Disease in Chronic Kidney Disease: Leading Cause of Mortality," as designed. I am claiming [up to .5 credit] _____ of *AMA PRA Category 1 Credit*™ for this activity.

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CME Evaluation

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PROGRAM OBJECTIVES:

Having completed this activity, I am better able to:	Strongly Agree				Strongly Disagree
Identify the risk factors that contribute to CVD and mortality in CKD patients.	5	4	3	2	1
Understand the consequences of vascular calcification and loss of elasticity and how these factors lead to CVD and mortality in CKD patients.	5	4	3	2	1
Discuss how the proper management of secondary hyperparathroidism (SHPT) in CKD improves mineral metabolism, vascular elasticity, and inflammation that contribute to enhanced cardiovascular risk in these patients.	5	4	3	2	1
Review therapeutic measures that reduce cardiovascular risk factors in CKD patients and lead to improved survival outcomes.	5	4	3	2	1

OVERALL EVALUATION:

	Strongly Agree				Strongly Disagree
The information presented increased my awareness/understanding of the subject.	5	4	3	2	1
The information presented will influence how I practice.	5	4	3	2	1
The information presented will help me improve patient care.	5	4	3	2	1
The program was educationally sound and scientifically balanced.	5	4	3	2	1
Overall, the program met my expectations.	5	4	3	2	1
I would recommend this program to my colleagues.	5	4	3	2	1

The program was free of commercial bias or influence. [ ] Yes [ ] No (Please provide additional information below.)

If you anticipate changing one or more aspects of your practice as a result of your participation in this activity, please provide a brief description of how you plan to do so.

Please provide any additional comments pertaining to this activity (positives/negatives) and suggestions for improvement.

Please list any topics that you would like to be addressed in future educational activities.

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