

Optimizing the cost-effectiveness of treatment for chronic kidney disease-mineral and bone disorder

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Chronic kidney disease-mineral and bone disorder (CKD-MBD) is an important risk factor in patients with CKD, and some medications for treating CKD-MBD have been recently marketed. Because assessment of health-care cost-effectiveness is growing in importance with increases in health expenditures, several cost-effectiveness analyses for new medications such as sevelamer, lanthanum carbonate, cinacalcet hydrochloride, and paricalcitol have been conducted. The results of these analyses have stimulated discussion on the efficient use of these medications and, in some cases, have affected treatment recommendation. However, most of these studies had methodological problems, one of them being that the effectiveness of medications was estimated based on changes of surrogate parameters, such as vascular calcification or serum biochemistry values. Furthermore, even if cost-effectiveness analyses were based on a given clinical trial, the results might differ from country to country. To provide greater health benefits under limited health expenditures based on the results of cost-effectiveness analyses, it is necessary to confirm the effectiveness of medications through well-designed clinical trials having mortality as the primary end point. In addition, cost-effectiveness analyses need to be performed separately for each country.

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Many patients with end-stage kidney disease have disturbances in calcium and phosphorus homeostasis. These disorders contribute to vascular calcification and bone fragility, resulting in increased risk of fracture, cardiovascular disease, and death. In 2006, a systemic disorder of mineral and bone metabolism due to chronic kidney disease (CKD) was named CKD-mineral and bone disorder (CKD-MBD).¹ Recently, several new medications for treating CKD-MBD have been marketed. In Japan, the sale of sevelamer hydrochloride began in 2003. Subsequently, the use of cinacalcet hydrochloride, lanthanum carbonate, and bixalomer began in 2008, 2009, and 2012, respectively. These medications make it easier to control CKD-MBD and thus potentially improve survival and quality of life in patients with CKD. However, a concern is that these advancements in CKD-MBD treatment may profoundly increase total CKD-related costs.

The total annual cost for treating dialysis patients in Japan is estimated to cross ¥1.3 trillion, consuming approximately 4% of the total health expenditure.² The number of dialysis patients is increasing exponentially, and it surpassed 300,000 in 2011.³ This number is expected to continue increasing for the next several years. In addition, the average age of dialysis patients is increasing, and the proportion of patients with diabetes is growing. Because aging and diabetes render patients susceptible to several other diseases, the increase in the number of patients on dialysis, average age, and the number of patients with diabetes will increase the cost for patients on dialysis.

Because health expenses are increasing, the need to control health-care costs is increasing in many countries. Therefore, the evaluation of health-care cost-effectiveness is important. Many studies from Western countries have reported the cost-effectiveness of CKD-MBD-related medications.^{4–20} In contrast, only a few studies have investigated their cost-effectiveness in Japan.^{21,22} The results of cost-effectiveness analysis vary among races, health-care systems, and patient characteristics. Therefore, it is important to evaluate cost-effectiveness on the basis of original data obtained from each country.

Here we briefly explain the methods of assessing the cost-effectiveness of medications and then review the recent literature on cost-effectiveness analyses concerning the treatment of CKD-MBD.

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APPROACH TO ASSESS COST-EFFECTIVENESS

Cost-effectiveness is assessed by comparing cost and effectiveness. If one medication is cheaper and more effective than its comparator, it is cost-effective. If one medication is both costlier and more effective, it is necessary to assess the ratio of cost to effectiveness, termed incremental cost-effectiveness ratio (ICER). If ICER is within the threshold, the medication is accepted as cost-effective. This threshold varies in different countries. Conventionally, it is \$50,000–100,000 in the United States, £20,000–30,000 in the United Kingdom, and ¥5,000,000 in Japan.²³

The cost and effectiveness used in most cost-effectiveness analyses are estimated from short-term clinical trials, which evaluate the effect on survival or surrogate markers. Such trials are conducted because great expense and effort are needed to conduct long-term clinical trials, which investigate lifetime cost and effectiveness. Therefore, the quality of clinical trials, whose data are used to estimate cost-effectiveness, can affect the validity of the cost-effectiveness analysis.

The effectiveness evaluated in cost-effectiveness analyses often represents life-years or life-years adjusted for quality of life. The latter is called quality-adjusted life year (QALY). The score of QALY for complete health and death is 1 and 0, respectively. For example, QALYs of hemodialysis patients, patients with cardiovascular disease, or patients with fracture were 0.52–0.72, 0.57–0.97, or 0.75–0.92, respectively, when they survived for 1 year.^{5,6,8–22}

COST-EFFECTIVENESS ANALYSIS OF TREATMENT FOR CKD-MBD

Sevelamer

The cost-effectiveness of sevelamer has been evaluated and compared with calcium-containing phosphate binders in several studies on the basis of the results of randomized controlled trials (Table 1).^{4–9} Huybrechts *et al.* demonstrated that the use of sevelamer hydrochloride in hemodialysis patients was likely to be cost-effective in Canada⁷ and the United States,⁴ based on data of the Treat-to-Goal study.²⁴ Taylor *et al.*⁸ showed that treatment with sevelamer conferred clinical benefits with a modest investment of additional economic resources, based on data of the Renagel in New Dialysis (RIND) study.^{25,26} However, the primary end points in the Treat-to-Goal and RIND studies was reduction in the progression of coronary artery calcification but not a hard outcome, such as mortality. Although the RIND study demonstrated that mortality rate of patients treated with sevelamer was lower than that of patients treated with calcium-containing binders, mortality was only a secondary end point.

The Dialysis Clinical Outcomes Revisited (DCOR) trial²⁷ was a randomized controlled trial in which the primary end point was mortality. Although two cost-effectiveness analyses^{5,9} were performed on the basis of the DCOR trial, the results were contradictory. The first study demonstrated that the use of sevelamer hydrochloride as a first-line therapy was economically unattractive in hemodialysis patients.⁵ In contrast, the second study showed that treatment with

sevelamer was more cost-effective than treatment with calcium-containing binders.⁹ Although the first study included dialysis costs, ICER without dialysis cost in the first analysis (CAN \$77,600 per QALY gained) was much higher than ICER in the second study (£22,157 per QALY gained). The reason why the results differed is unclear. One reason may be that the difference of annual cost between calcium-containing phosphate binders and sevelamer in the first study (CAN\$4125) was larger than that in the second study (£1888). Furthermore, because the DCOR trial did not show a significant effect of sevelamer on mortality (HR 0.93, 95% CI 0.79–1.10, $P = 0.40$), the conclusion that sevelamer is cost-effective compared with calcium-containing binders appears to be inconsistent with the DCOR results. Further clinical trials are necessary to elucidate whether sevelamer hydrochloride is cost-effective compared with calcium-containing phosphate binders.

One study was devoted to a cost-effectiveness analysis of sevelamer in pre-dialysis patients.¹⁰ In that study, the authors concluded that sevelamer as a first-line therapy was cost-effective compared with calcium carbonate. Because the study was based on the INDEPENDENT-CKD study,²⁸ which demonstrated improved survival with sevelamer compared with calcium carbonate, this cost-effectiveness analysis seems to be valid. However, the sample size of the trial was small and the duration relatively short.

Lanthanum carbonate

Cost-effectiveness analyses of lanthanum carbonate are shown in Table 2.^{10–13,21} In each case, lanthanum carbonate was analyzed as additional therapy. Brennan *et al.*¹⁰ demonstrated that lanthanum carbonate was likely to be cost-effective in hemodialysis patients who did not achieve control of hyperphosphatemia with calcium-containing binders. However, their study did not include sevelamer hydrochloride. We conducted a clinical study investigating the effect of lanthanum carbonate on serum phosphorus levels in hemodialysis patients who did not achieve control of hyperphosphatemia with conventional medications, including sevelamer hydrochloride; subsequently, on the basis of the clinical study, we performed a cost-effectiveness analysis.²¹ The analysis revealed that additional administration of lanthanum carbonate would be cost-effective. Another study analyzed cost-effectiveness using the same model as Brennan *et al.*¹⁰ in the Canadian perspective and showed a similar result.¹²

Vegter *et al.*¹¹ evaluated the cost-effectiveness of lanthanum carbonate in pre-dialysis patients. In their study, the use of lanthanum carbonate reduced cost by £339 and gained 44.1 QALYs. This study also investigated the cost-effectiveness of the medication in dialysis patients. They concluded that additional therapy with lanthanum carbonate conferred good value for money, irrespective of dialysis status.

Two studies compared lanthanum carbonate with sevelamer. The study by Park *et al.*¹³ showed that lanthanum carbonate is cost-effective compared with sevelamer

Table 1 | Cost-effectiveness analyses of sevelamer

	Country	Target population	Dialysis cost	Primary outcome of the clinical trial	ICER
Huybrechts ⁴	USA	HD	Excluded	Vascular calcification	\$2200 ^a
Manns ⁵	Canada	HD	Included	Mortality	CAN\$157,500
			Excluded		CAN\$77,600
Taylor ⁶	UK	HD	Excluded	Vascular calcification ^b	£27,120
Huybrechts ⁷	Canada	HD	Excluded	Vascular calcification	CAN\$12,384 ^a
Thompson ⁸	UK	HD	Excluded	Mortality	£23,878
Bernard ⁹	UK	Pre-dialysis	Excluded	Mortality	£22,157

Abbreviations: HD, hemodialysis; ICER, incremental cost-effectiveness ratio.

^aPer life-year gained.

^bClinical effects in the cost-effectiveness analysis were based on mortality.

Table 2 | Cost-effectiveness analyses of lanthanum carbonate

	Country	Target population	Dialysis cost	Primary outcome of the clinical trial	ICER
Brennan ¹⁰	UK	HD	Excluded	P levels	£25,033
Goto ²¹	Japan	HD	Excluded	P levels	\$34,896
Vegter ¹¹	Canada	HD	Excluded	P levels	£6900
		Pre-dialysis	Included		Dominant
Vegter ¹²	UK	HD	Excluded	P levels	CAN\$13,200
Park ¹³	USA	HD	Excluded	P levels	\$24,724 ^a

Abbreviations: HD, hemodialysis; ICER, incremental cost-effectiveness ratio; P, phosphorus.

^avs. sevelamer hydrochloride.

Table 3 | Cost-effectiveness analyses of cinacalcet hydrochloride

	Country	Target population	Dialysis cost	Primary outcome of the clinical trial	ICER	Rate of PTx (%/year)
Garside ¹⁴	UK	HD	Excluded	PTH levels	£61,890	10
Ray ¹⁵	USA	HD	Excluded	PTH levels	\$17,275	Control 4.1
						Cinacalcet 0.3
Eandi ¹⁶	Italy	HD	Excluded	PTH levels	€31,616	0.09 ^a
Komaba ²²	Japan	HD	Excluded	PTH levels	\$352,631	100
					\$21,613	0
Boer ¹⁷	USA	HD	Excluded	Vascular calcification ^b	\$54,560	1.2

Abbreviations: HD, hemodialysis; ICER, incremental cost-effectiveness ratio; PTH, parathyroid hormone; PTx, parathyroidectomy.

^aAdjusted by the baseline distribution of calcium, phosphorus, and parathyroid hormone levels.

^bClinical effects in the cost-effectiveness analysis were based on calcium, phosphorus, and parathyroid hormone levels.

hydrochloride in end-stage renal disease patients. However, the difference in efficacy between lanthanum carbonate and sevelamer hydrochloride was only 0.025 QALYs, and the difference of serum phosphorus levels was only 0.26 mg/dl in the clinical trial that was the basis of this cost-effectiveness analysis. Because it remains unclear whether lanthanum carbonate is superior to sevelamer hydrochloride, it seems too early to conclude that lanthanum carbonate is cost-effective compared with sevelamer. Another study compared Canadian costs alone assuming that the efficacies were the same.¹² The result was that lanthanum carbonate therapy was 23% less expensive. However, because drug prices vary by country and/or insurance system, results may differ from one country to the other.

The major limitation of these studies is that the effectiveness of lanthanum carbonate is estimated based on changes of a surrogate marker. The cost-effectiveness needs to be confirmed by an analysis based on a clinical trial with mortality as the primary outcome.

Cinacalcet hydrochloride

The cost-effectiveness of cinacalcet hydrochloride is controversial (Table 3).^{14–17,22} A study by Garside *et al.*¹⁴ demonstrated that cinacalcet hydrochloride was unlikely to be considered cost-effective. In contrast, the results of three other studies led to the conclusion that the use of cinacalcet was likely to be cost-effective.^{15–17} One of the main explanations for this discrepancy could be a difference in the indication for parathyroidectomy in a simulation model to estimate cost and effectiveness (Table 3). We performed analyses in two types of cohorts separately: those who were eligible and those who were ineligible for parathyroidectomy.²² We found that cinacalcet was likely to be cost-effective only for those patients who were ineligible for parathyroidectomy. Narayan *et al.*²⁹ compared costs and the ratio of cost to effectiveness directly between cinacalcet and parathyroidectomy. The authors concluded that cinacalcet was not cost-effective except for those patients in whom an only brief stay on dialysis therapy was expected. Collectively, these

Table 4 | Cost-effectiveness analyses of paricalcitol

	Country	Target population	Dialysis cost	Primary outcome of the clinical trial	ICER
Rosery ¹⁸	Germany	HD	Excluded ^a	Mortality ^b , hospitalization ^b	Dominant
Nuijten ¹⁹	USA	Pre-dialysis	Included	Mortality ^b , hospitalization ^b , proteinuria	Dominant
Nuijten ²⁰	USA	Pre-dialysis	Included	Mortality ^b , hospitalization ^b	£6933

Abbreviations: HD, hemodialysis; ICER, incremental cost-effectiveness ratio.

^aMay include dialysis cost in hospital stay.

^bData were derived from observational studies.

findings indicate that cinacalcet represents good economic value only for patients who are ineligible for parathyroidectomy, patients whose dialysis duration is expected to be short because of transplantation, and so on. In addition, because all estimates of the effectiveness of cinacalcet hydrochloride were based on changes of a surrogate marker, it is necessary to confirm the cost-effectiveness by an analysis based on the Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) trial³⁰ that investigated the effect of cinacalcet on a composite cardiovascular end point, including mortality.

Vitamin D receptor activators

To the best of our knowledge, all cost-effectiveness analyses of vitamin D sterols in patients with CKD compared paricalcitol with calcitriol or alfacalcidol (Table 4).^{18–20} These studies demonstrated that the use of paricalcitol is likely to be cost-effective. However, because the effectiveness of paricalcitol in these cost-effectiveness analyses was derived from observational studies alone, it should be considered that the cost-effectiveness of paricalcitol remains unclear.

CONCLUSION

We reviewed cost-effectiveness analyses of therapies for CKD-MBD. Although the cost-effectiveness of some medications for CKD-MBD has been examined, it is necessary to confirm the results of these studies with future cost-effectiveness analyses based on more well-designed clinical trials. We hope that this review will stimulate a broader discussion of cost-effective therapies for CKD-MBD, with the ultimate goal to provide optimal health benefits for patients with CKD despite limited health budgets.

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