Policy changes and impact rises: Erythropoietin Payment Policy on Cardiovascular Outcomes of Peritoneal Dialysis Patients

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Research article

Keywords: erythropoietin, cardiovascular disease, peritoneal dialysis, diabetes mellitus, end-stage renal disease

Posted Date: March 26th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-18616/v1

Abstract

Background and Purposes

The change in reimbursement policy of erythropoietin application to peritoneal dialysis (PD) patients by Taiwan National Health Insurance (NHI) system provided a natural experimental venue to examine whether cardiovascular risk differs while keeping hematocrit (Hct) below 30% or over 30%. This study intended to analyze the impact of loosening erythropoietin payment criteria for PD patients on their cardiovascular outcomes.

Methods

Two cohorts of incident PD patients before and after the relaxation of NHI's erythropoietin payment criteria were identified as Cohort 1 and Cohort 2, respectively, and further matched by propensity scores and then followed up for cardiovascular events. There were 1,759 patients in Cohort 1 and 2,981 patients in Cohort 2. After propensity score matching, 1,754 subjects were selected from each cohort. The outcome measures were cardiovascular events and were analyzed through Cox regressions.

Findings and Conclusion

For the composite cardiovascular endpoint, Cohort 2 patients had significantly lower risk than Cohort 1. The risk reduction was observed only in diabetic patients. After loosening erythropoietin payment criteria, less cardiovascular risks were observed, particularly for diabetic patients. It is concluded that for diabetic PD patients, maintaining a Hct level higher than 30% is crucial for reducing the cardiovascular risk.

1. Introduction

Erythropoietin is a major regulatory hormone of erythrocyte production that is produced from kidney. For chronic kidney disease (CKD) patients, erythropoietin production from kidney decreases. In addition, shorten erythrocyte survival and chronic inflammatory status contribute to anemia. Administration of exogenous erythropoietin for CKD patients, especially who receive dialysis, is the standard treatment of anemia.

In the past, with the use of erythropoietin, the practice tended to increase hematocrit (Hct) target to "normal level" (i.e., 40.5% for male and 36% for female). However, more recent large, randomized outcome trials [1–3] show that elevated Hct to more than 36% compared to 30–36% is associated with higher cardiovascular risk for CKD patients. These findings led to the limitation of Hct upper bound. However, what is an optimal Hct target is still debatable. The recommendations from National Kidney Foundation-Kidney Disease Outcomes and Quality Initiative [4] and Taiwan's nephrology professionals [5] both suggest keeping the level of Hct between 33 and 36%.

The public statement of the European Medical Agency in 2007 concluded that a target Hct range is 30–36% [6]. U.S. Food and Drug Administration recommended to reduce or interrupt erythropoietin if

hematocrit approaches or exceeds 33% for dialysis patients in 2011 safety announcement [7]. The recommendation from Kidney Disease Improving Global Outcome in 2012 was to maintain Hct below 34.5% [8]. Accordingly, a range from 30–36% might be considered the least bandwidth to accommodate these recommendations.

In order to reduce the cost of providing end-stage renal disease (ESRD) treatments while maintaining or preferably improving patient care, the U.S. Center for Medicare and Medicaid (CMS) recently implemented the ESRD Prospective Payment System, known as the “expanded ESRD bundle” on January 1, 2011 [9]. In response to a quality incentive program (QIP) required by the Congress, two quality measures of anemia management were established to identify poor performance, patients with a hemoglobin (Hb) level less than 10 g/dL and a Hb level greater than 12 g/dL. [9] These Hb levels are equivalent to the levels of Hct less than 30% and beyond 36% since conversion between Hb and Hct is that 1 g/dL in Hb is equal to 3% in Hct. However, the CMS retired the Hb less than 10 g/dL measure in its later QIP requirements [10, 11]. The dialysis facilities would receive no penalties for Hb levels lower than 10 g/dL, and patients with Hb level lower than 10 g/dL might be spotted more often in the future. The elimination of penalties for lower bound of Hb levels has indeed removed the financial incentives to provide costly erythropoietin and raised some concerns about patient care [12]. Nevertheless, whether patients with a Hb level lower than 10 g/dL or Hct level lower than 30% will be associated with lower or higher risk of adverse events will be a logical inquiry warranted for investigation.

Limited studies had reported cardiovascular events or mortality associated with Hct levels lower than 30%. By comparing dialysis patients maintaining Hct below 30% to those with 30–36%, no significant difference was found [13–15]. While more recent studies [1–3] comparing the risk of pushing Hct levels over 36% with that of between 30–36% had a large sample size of more than twelve hundreds with a follow-up period more than fourteen months, these early studies had a relatively small sample size of 152 patients or less and a short follow-up period of six to nine months. Moreover, their research emphases were not specifically designed and dedicated to this research issue. Recently, the change in reimbursement policy of erythropoietin application to peritoneal dialysis patients by Taiwan National Health Insurance (NHI) system provided a natural experimental venue for examining this clinical research issue.

The incidence and prevalence rates of ESRD in Taiwan have been ranked at the top internationally since 2001 [16], and this has put immense burdens of caring and funding for ESRD patients on its NHI system. The low renal transplant rate, less than 1% annually [17] results in nearly all of Taiwan’s ESRD patients on dialysis treatments to prolong their lives, and more than 93.5% undergo hemodialysis treatments in 2004 [18]. In order to increase peritoneal dialysis (PD) utilization, Taiwan’s NHI had introduced a series of PD encouragement policies since 2005, and loosening the reimbursement criteria on November 1, 2006 was one of these important encouragement policies. Before November 1, 2006 the treatment of erythropoietin to a PD patient could only be reimbursed by NHI if the patient’s Hct was ≦ 30% and with a maximal monthly erythropoietin dosage of epoetin alfa/beta 20,000 units (U) or darbepoietin alfa 100 μg. After November 1, 2006 the level of applying erythropoietin was relaxed to Hct ≦ 36% with the same maximal

monthly erythropoietin dosage. Subsequent to the introduction of the erythropoietin criteria relaxation, the Hct levels for both prevalent and incident PD patients were observed an increase from 28–29% to 30–31%. The [19–21] main purpose of our study is to analyze the impact of loosening erythropoietin application criteria for PD patients to understand if less cardiovascular events may occur when maintaining Hct between 30–31% as compared to 28–29%.

2. Methods

2.1 Ethics statement

Data resource was based on the National Health Insurance Research Database (NHIRD). [22] Researchers can access NHIRD data after ethical and scientific review processes. Prior to applying, the study has been approved by the ethical review board of National Taiwan University Hospital (NTUH-REC No.201406018W). There are 27 institutional review boards capable of issuing approvals, and all are supervised and regulated by the Taiwan Ministry of Health and Welfare. To protect individuals' confidentiality, all datasets in the Data Science Centre are pseudonymized. Personal ID, birth date, and names are encrypted, and this de-identification process was approved by an independent third party. We performed data analysis in the branches of the Data Science Centre. The analyzed results were also examined by the Data Science Centre before exporting. The Institutional Review Board had verified the anonymity of data analysis performed in this study. All research procedures followed the directives of the Declaration of Helsinki.

2.2 Study Design

This is an observational study to compare the cardiovascular events of two cohorts of the newly treated (incident) PD patients before and after the relaxation of NHI's erythropoietin payment criteria. Cohort 1 included dialysis patients who started to receive maintenance PD treatments during a specified period of 28 months before the relaxation of NHI's erythropoietin payment criteria. To ensure an adequate observation period, this cohort was followed up for additional 14 months after the month of the cohort's last patient enrollment. Cohort 2 included incident dialysis patients who started to receive maintenance PD treatments within a 28-month time interval after the relaxation of NHI's erythropoietin payment criteria. Additional 14-month follow-up observations were also made after the month of the cohort's last patient enrollment. We set a 6-month time lag between the initiation of relaxing erythropoietin payment criteria and the time that the first enrollment of patients in Cohort 2 in order to accommodate possible adaptation of physician prescribing practices to the new policy.

Because the potential imbalances in the distributions of many measured and unmeasured baseline covariates exist between the two cohorts, researchers have to employ the propensity score (PS) analysis, developed by Rosenbaum et al. [23] Thus, the influence of any potential enrollment biases between these two cohorts was attenuated through a PS matching approach and identification of patients with comparable characteristics in the two cohorts. This study defined PS as the probability of a patient having experienced a cardiovascular event. Patients in Cohort 1 and 2 were matched with PS scores

estimated by age, sex and a comorbidity index with the nearest neighbor-greedy approach. The comorbidity index was developed by Liu et al. [24] specifically for U.S. Medicare dialysis population and had been validated in Taiwanese dialysis patients [25].

After matching with PS, patients were followed up till experiencing either one of the following three events: 1) the occurrence of cardiovascular endpoints, or 2) change to hemodialysis, or 3) data cut-off point (October 31, 2006 for Cohort 1; October 31, 2010 for Cohort 2), whichever occurred earlier. Survival analysis models were then employed to investigate the differences in the risk of cardiovascular events between the two cohorts of incident PD patients. Baseline demographics and comorbid conditions were used as covariates in the statistical analyses. Monthly erythropoietin doses administered to patients of Cohort 1 and Cohort 2 during the follow-up period were compared to examine whether there existed a difference in the monthly erythropoietin dosage administered between the two cohorts of incident PD patients. In calculation of erythropoietin dosage, while erythropoietin alfa and erythropoietin beta were considered equivalent, darbepoietin alfa was converted into erythropoietin alfa with 1ug of darbepoietin alfa equal to 200U of erythropoietin alfa [26].

Cardiovascular risk could be affected by treatments with concomitant medications related to cardiovascular comorbidities. Patients taking medications related to cardiovascular comorbidities during the follow-up period in two cohorts were also examined. The concomitant medications related to cardiovascular comorbidities were identified by corresponding ATC code, including acetylsalicylic acid (B01AC06) or clopidogrel (B01AC04), angiotensin converting enzyme inhibitors (C09A) or angiotensin receptor blockers (C09C), beta blockers (C07), calcium channel blockers (C08) and statins (C10AA). A patient received the medication for any three months during the follow-up period would be considered under the treatments of concomitant medications related to cardiovascular comorbidities.

Finally, in addition to administering erythropoietin, because the patient Hct level could also be affected by the usages of iron and red-cell transfusion, iron and red-cell transfusion for patients in the two cohorts were examined to determine if differences in the usages of iron and red-cell transfusion existed between the two cohorts.

2.3 Patient selection

Incident PD patients were identified from the claim data of entire beneficiaries covered by the NHI system from 2003 to 2010. Collection and analysis of the NHI claimed data were approved by the National Taiwan University Hospital Human Research Ethics Committee. The analyses were performed on de-identified data extracted from the NHI research database compiled by Taiwan National Health Research Institutes. A patient receiving over 90-day consecutive dialysis treatments and with PD on the day 90^{th} and thereafter is considered as an incident PD patient in this study. Cohort 1 recruited patients with the 90^{th} dialysis day between May 1, 2003 and August 31, 2005, and Cohort 2 recruited patients with the 90^{th} dialysis day between May 1, 2007 and August 31, 2009. Young patients under 20 were excluded because

the comorbidities were different between pediatrics and adults. There were 1,759 patients in Cohort 1 and 2,981 patients in Cohort 2. After the PS matching, each cohort contained only 1,754 patients.

2.4 Statistical Analyses

The primary outcome measure is a composite cardiovascular endpoint, defined as myocardial infarction, heart failure hospitalization, stroke or death. Myocardial infarction was defined by *International Classification of Diseases, Ninth Revision* (*ICD-9*) code 410, 411 in the hospital discharge diagnosis. Heart failure hospitalization was defined by *ICD-9* hospital discharge diagnosis codes 398.91, 422, 425, 428, 402.x1, 404.x1, 404.x3, and V42.1. Stroke was defined by *ICD-9* hospital discharge diagnosis codes 433, 434, 436, 437.0 and 437.1. For primary outcome measure, all patients in both cohorts were followed up to the occurrence of myocardial infarction, heart failure hospitalization, stroke or death, whichever occurred earlier. Secondary outcomes include myocardial infarction, heart failure hospitalization, stroke and death. Each patient was followed up to the occurrence of each cardiovascular event. Data on patients who did not have an event were censored at the data cut-off point or transition to hemodialysis, whichever occurred earlier.

The selection and analyses of primary and secondary endpoints of cardiovascular risk in our study were the same as previous large-scale studies [1-3]. In addition to cardiovascular events, death was also considered an important clinical endpoint in the evaluation of cardiovascular risk because reducing mortality is an ultimate goal of reducing cardiovascular risk. Using a composite primary endpoint with each component evaluated as the secondary endpoint analysis is commonly adopted by many clinicians [2, 3], such as pivotal studies of new drug applications. This allows a thorough evaluation of contribution of each component of composite primary endpoint and avoiding any biases introduced by one of the dominating component.

Cox proportional hazards model was employed to estimate the cardiovascular risk between the two cohorts. Estimated hazard ratios (HRs) for Cohort 2 relative to Cohort 1 and 95% confidence intervals (CIs) were calculated. In order to obtain more insightful results, patients were further stratified by diabetic status. Cox regression analyses for diabetic and non-diabetic patients were performed separately. All analyses were performed using SAS software, version 9.1.

3. Results

Table 1 shows the baseline demographics and comorbid conditions of the equal number (1,754) of incident PD patients in the two cohorts. No statistically significant differences observed suggest that both cohorts appear to be similar in terms of age, gender and comorbid conditions in baseline. The comparisons of using concomitant medications related to cardiovascular comorbidities in the two cohort patients during the follow-up period are also presented, showing no statistical differences in the usage of any concomitant medication related to cardiovascular comorbidities between the two cohorts observed.

Table 1

Baseline demographics and concomitant medications during the follow-up period in Cohort 1 and Cohort 2 after matched with propensity score

	Matched Cohort 1[a] (n = 1,754)		Matched Cohort 2[a] (n = 1,754)		P value
Baseline demographics					
Sex					0.84
Female	994	(56.7)	991	(56.5)	
Age	52.96 ± 15.36		52.87 ± 15.02		0.33
20–39	326	(18.6)	327	(18.6)	
40–49	390	(22.2)	384	(21.9)	
50–59	431	(24.6)	444	(25.3)	
60–69	320	(18.2)	324	(18.5)	
≧ 70	287	(16.4)	275	(15.7)	
Comorbidity Index	2.52 ± 1.72		2.52 ± 1.79		0.80
0	401	(22.9)	401	(22.9)	
1	268	(15.3)	269	(15.3)	
2	324	(18.5)	323	(18.4)	
3	245	(14.0)	243	(13.9)	
4	180	(10.3)	182	(10.4)	
5	148	(8.4)	148	(8.4)	
6	94	(5.4)	94	(5.4)	
7	49	(2.8)	50	(2.9)	
8	24	(1.4)	23	(1.3)	
9	10	(0.6)	10	(0.6)	
≧ 10	11	(0.6)	11	(0.6)	
Baseline Comorbidity					
Atherosclerotic heart disease	327	(18.6)	320	(18.2)	0.49
Congestive heart failure	192	(11.0)	192	(11.0)	1.0

	Matched Cohort 1[a] (n = 1,754)		Matched Cohort 2[a] (n = 1,754)		P value
Cerebrovascular accident/transient ischemic attack	273	(15.6)	268	(15.3)	0.67
Peripheral vascular disease	250	(56.7)	253	(56.5)	0.76
Other cardiac disease	220	(12.5)	223	(12.7)	0.75
Chronic obstructive pulmonary disease	106	(6.0)	110	(6.3)	0.59
Gastrointestinal bleeding	212	(12.1)	207	(11.8)	0.65
Liver disease	200	(11.4)	204	(11.6)	0.66
Dysthymia	60	(3.4)	56	(3.2)	0.48
Cancer	149	(8.5)	151	(8.6)	0.80
Diabetes	581	(33.1)	584	(33.3)	0.82
Hypertension	1,297	(74.0)	1,305	(74.4)	0.70
Atrial fibrillation	19	(1.1)	15	(0.9)	0.33
Coronary artery bypass graft	134	(7.6)	128	(7.3)	0.59
Myocardial infarction	22	(1.3)	21	(1.2)	0.89
Medications – concomitant					
Acetylsalicylic acid or clopidogrel	1,369	(78.1)	1,355	(77.3)	0.39
ACEIs or ARBs	637	(36.3)	631	(36.0)	0.38
Beta blockers	589	(33.6)	586	(33.2)	0.48
CCB	683	(38.9)	693	(39.5)	0.37
Statins	509	(29.0)	504	(28.7)	0.32
Medications – iron/red cell transfusions/erythropoietin					
Oral iron usage	72	(4.1)	69	(3.9)	0.63
IV iron usage	794	(45.3)	772	(42.0)	0.61
Red-cell transfusions percentage	194	(11.1)	170	(9.7)	0.09
Red-cell transfusions unit per patient per month	0.059 ± 0.216		0.044 ± 0.172		0.033
Oral iron doses per patient per month (mg)	25.06 ± 129.66		23.39 ± 125.0		0.23

	Matched Cohort 1[a] (n = 1,754)		Matched Cohort 2[a] (n = 1,754)		P value
IV iron doses per patient per month (mg)	106.54 ± 92.29		98.91 ± 89.38		0.19
Erythropoietin[b] usage per patient per month (U)	10,588[c]	(7,750 – 13,280)[d]	12,379[c]	(8,580 – 14,570)[d]	< 0.0001
Values expressed with a plus/minus sign are the mean ± SD and were tested by t-test. All other values, unless specifically noted, are the number (percentage) of patients and were tested by proportion z-test.					
Abbreviations: ACEIs: angiotensin converting enzyme inhibitors; ARBs: angiotensin receptor blockers; CCB: calcium channel blockers; IV: intravenous.					
[a] Patients in Cohort 1 and 2 were matched with propensity score by age, sex and comorbidity index using Greedy method.					
[b] Including erythropoietin alfa, erythropoietin beta and darbepoietin alfa. Erythropioetin alfa and beta was considered equivalent. Darbepietin alfa 100ug was considered equivalent to erythropoietin 20,000u according to NHI's reimbursement criteria.					
[c] Numbers shown are medians and were tested by Wilcoxon Rank Sum test					
[d] Numbers shown are interquartile range					

The median monthly erythropoietin dosage was significantly higher in Cohort 2 than in Cohort 1 (12,739U versus 10,588U, $p < 0.0001$). The usages of iron supplements (both oral and intravenous) and red-cell transfusions were comparable in both cohorts.

For the composite cardiovascular endpoint, the risk in Cohort 2 was significantly lower (HR, 0.83; 95% CI, 0.69 to 0.98, Table 2) after adjusting age, sex, comorbidity index, diabetes mellitus (DM), hypertension, history of coronary artery bypass graft and congestive heart failure. For each cardiovascular endpoint, the risk reduction in Cohort 2 did not reach any statistical significance. With regard to the subgroup analysis (Table 3), for non-diabetic patients, no significant difference in either the composite cardiovascular endpoint or any individual cardiovascular endpoint was observed between the two cohorts. However, for diabetic patients, the risk of composite cardiovascular endpoint was significantly lower in Cohort 2 (HR, 0.74; 95% CI, 0.60 to 0.93). In addition, the risk of stroke (HR, 0.61; 95% CI, 0.39 to 0.98) and heart failure hospitalization (HR, 0.72; 95% CI, 0.54 to 0.99) were also significantly lower in Cohort 2.

Table 2

Results of primary and secondary endpoints (Hazard Ratio: matched Cohort 2/ matched Cohort 1)

Variable	Matched Cohort 1 [a] (n = 1,754)	Matched Cohort 2 [a] (n = 1,754)	Hazard Ratio [b] (95% CI)	P Value
Primary endpoint: cardiovascular composite endpoint	299 (17.1)	261 (14.9)	0.82 (0.69 to 0.98)	0.04
Secondary endpoints				
Myocardial infarction	40 (2.3)	36 (2.1)	0.81 (0.48 to 1.19)	0.20
Stroke	58 (3.3)	45 (2.6)	0.72 (0.50 to 1.12)	0.15
Heart failure hospitalization	173 (9.9)	162 (9.2)	0.76 (0.65 to 1.09)	0.17
Death	91 (5.2)	89 (5.1)	0.92 (0.68 to 1.24)	0.59

Values expressed as number (percentage) of patients.

[a] patients in Cohort 1 and 2 were matched with propensity score by age, sex and comorbidity index using Greedy method.

[b] adjusted by age, sex, comorbidity index, diabetes, hypertension, history of coronary artery bypass graft and congestive heart failure

Table 3

Subgroups analysis for diabetic versus non-diabetic patients (Hazard Ratio: matched Cohort 2/ matched Cohort 1)[a]

	DM patients [b]			non-DM patients [b]		
	HR [c]	95% CI	P value	HR [c]	95% CI	P value
Primary endpoint						
Cardiovascular composite endpoint	0.74	(0.60 to 0.93)	0.006	0.97	(0.74 to 1.27)	0.82
Secondary endpoints						
Myocardial infarction	0.67	(0.36 to 1.15)	0.19	0.86	(0.33 to 2.25)	0.76
Stroke	0.61	(0.39 to 0.98)	0.04	1.02	(0.51 to 2.04)	0.93
Heart failure hospitalization	0.72	(0.54 to 0.99)	0.04	1.06	(0.74 to 1.51)	0.76
Death	1.07	(0.73 to 1.58)	0.73	0.79	(0.49 to 1.26)	0.27

[a] patients in Cohort 1 and 2 were matched with propensity score by age, sex and comorbidity index using Greedy method.

[b] DM patients in Cohort 1 was 581 and in Cohort 2 was 584 patients, while non-diabetic patients in Cohort 1 was 1173 and in Cohort 2 was 1170 patients.

[c]adjusted by age, sex, comorbidity index, hypertension, history of coronary artery bypass graft and congestive heart failure

4. Discussion

No statistically significant difference was observed for baseline comorbidities and concomitant medications in the follow-up period between the matched Cohort 1 and Cohort 2 (Table 1). This suggests that both cohorts had similar cardiovascular risk factors. After loosening erythropoietin payment criteria, the erythropoietin dosage increased and cardiovascular risk decreased. The reduction in cardiovascular risk was observed only in diabetic patients, however. Among diabetic patients, significant risk reduction was found not only in composite cardiovascular endpoint, but also in secondary endpoints including stroke and heart failure hospitalization. Since similar percentages of patients in matched Cohort 1 and Cohort 2 received oral and intravenous iron, and the oral and intravenous iron dosage was also comparable between these two cohorts, it is reasonable to assume that higher Hct in matched Cohort 2

might result from higher erythropoietin dosage. And the reduction in cardiovascular risk in matched Cohort 2 may be related to higher erythropoietin dosage and adequate Hct range.

While the findings demonstrating that pushing Hct to more than 36% compared to 30–36% tend to increase cardiovascular risk [1–3, 7] have been widely accepted and recommended, lack of sufficient evidences to present whether there exist differences in cardiovascular risk by maintaining Hct levels below 30% relative to 30–36%. A few studies with a small sample and a short follow-up period showed no significant difference in cardiovascular risk or mortality for patients maintaining Hct below 30% compared to those maintaining 30–36%. [13–15] Thus, these limitations prevent investigators to detect the potential difference in cardiovascular risk. On the contrary, our national study showed that lower cardiovascular risk is associated with increasing Hct from 28–29% to 30–31% for incident PD patients. The number of subjects in our study was 3508, and the median follow-up duration was 23 months. The sample size and follow up duration were comparable to those more recent large-scale studies [1–3], where the sample sizes were between 1265 and 4038 and the median follow-up durations between 14 and 29 months.

Although no Hct data reported in the NHI beneficiaries claim database had led to no direct observations for patients' Hct levels of this study, our study used whole NHI's population (census) data and government documents published Hct statistics for NHI's dialysis patients. [19–21] Moreover, from governmental published data the Hct of both prevalent and incident PD patients were very similar (prevalent PD versus incident PD, from 2005 to 2008: 28.9–30.4% versus 29.1 to 30.4%) and the Hct of both PD patients with DM and without DM were very close as well (DM versus non-DM, from 2003 to 2008: 28.5–30.6% versus 28.3–30.3%). Therefore, we assumed that the Hct of incident PD patients in our study was similar to the Hct of PD patients reported by the government documents. After loosening the erythropoietin payment criteria, the Hct of both prevalent and incident PD patients increased from 28–29% to 30–31% [19–21].

In our study, the median erythropoietin dosage in Cohort 2 (12,739U) was significantly higher than that in Cohort 1 (10,588U), that is, more than 20% increase after loosening the erythropoietin reimbursement criteria. Given that the usages of iron supplements (both oral and intravenous) and red-cell transfusions were comparable in both cohorts, increased erythropoietin usage supports the assumption that the Hct of incident PD patients also increased after loosening the erythropoietin payment criteria.

Because the reduction in cardiovascular risk was observed only in diabetic patients, the difference in cardiovascular event risk reduction between diabetic and non-diabetic patients might not be the result from Hct difference; the Hct was similar between diabetic and non-diabetic incident PD patients from 2003 to 2008, with 28.5–30.6% versus 28.3–30.3% [21]. Rather than analyzing the two subgroups (DM and non-DM) separately through Cox proportional hazards model, we re-analyzed the non-stratified data through Cox proportional hazards model adding two more variables, one dichotomous variable for differentiating diabetic status and the other is the interaction term between diabetic status and cohort period. While the estimate of diabetic status represented the cardiovascular risk of diabetic patients

relative to that of non-diabetic patient in time period of Cohort 1, the estimate of the interaction term measured the change in cardiovascular risk of diabetic patients relative to the change of non-diabetic patients in the time period of Cohort 2 compared to the time period of Cohort 1. The results showed that the incident PD patients with DM had significant high cardiovascular risk than those non-DM by 78% (HR, 1.78; 95% CI 1.40 to 2.30, Table 4). However, while no significant change in cardiovascular risk for our non-diabetic PD patients in Cohort 2 (HR, 0.974; 95% CI, 0.84 to 1.05), the cardiovascular risk of our diabetic PD patients was significantly reduced by 22% in Cohort 2 (HR, 0.78; 95% CI, 0.61 to 0.94). This means that the cardiovascular risk of incident PD patients with DM was 39% (1.78⁄0.78 = 1.39) higher than that of incident PD patients without DM in the time period of Cohort 2, reduced from 78% higher in the time period of Cohort 1. Further examining the erythropoietin dosages used by the diabetic patients and non-diabetic patients in the two cohorts, no significant difference was observed between these two patient groups in either cohort (DM versus non-DM median in Cohort 1: 10,726U versus 10,525U, p = 0.09; in Cohort 2: 12,254U versus 12,310U, p = 0.17). Given these findings and similar Hct levels between the diabetic and non-diabetic PD patients, the increases in erythropoietin dosage and the Hct levels from below 30% to above 30% might benefit PD dialysis patients with DM in terms of reducing cardiovascular risk but have no impact on the cardiovascular risk of non-diabetic PD patients. This suggests that for non-diabetic PD patients no difference in cardiovascular risk is observed by maintaining Hct level below 30% or above 30%. However, for PD patients with DM maintaining a Hct level higher than 30% is crucial for reducing the cardiovascular risk. This provides important implication for policy makers since how to cost-effectively use healthcare resources and improve patient care is one of core challenges facing by health policy makers around the world, including Taiwan and U.S. as well. Based on these findings, Taiwan's NHI policy makers should reconsider the relaxation of NHI's reimbursement criteria targeting only for diabetic PD patients rather than universally applied it. In this way, the NHI could spend lesser and improve diabetic PD patient care by reducing their cardiovascular risk. As for U.S. policy making, it is possible that more patients would have Hb less than 10 g/dL (i.e., Hct 30%) and thus higher cardiovascular risk might be incurred for ESRD patients with DM after the elimination of the Hb less than 10 g/dL measure in its QIP requirements. Whether a lower bound of Hct/Hg level should be restored for these ESRD patients with DM in order to reach a balance between cost reduction and improvement on patient care is a critical issue to be examined by U.S. policy makers.

Table 4

Cox regression of primary endpoint accommodating time-vary risks on DM status

Variable	Estimate	P value	Hazard Ratio [a] (95% CI)
Cohort 2	-0.03	0.15	0.974 (0.84 to 1.05)
Age (40–49)	0.08	0.58	1.08 (0.80 to 1.46)
Age (50–59)	0.42	0.005	1.53 (1.15 to 2.03)
Age (60–69)	0.65	< 0.0001	1.92 (1.46 to 2.55)
Age (≧ 70)	0.84	< 0.0001	2.31 (1.82 to 2.90)
Gender	-0.06	0.56	0.94 (0.80 to 1.13)
Comorbidity index	0.11	< 0.0001	1.12 (1.07 to 1.17)
DM	0.58	< 0.0001	1.78 (1.40 to 2.30)
Hypertension	0.07	0.48	1.08 (0.87 to 1.34)
History of coronary artery bypass graft	0.33	0.008	1.39 (1.09 to 1.77)
History of congestive heart failure	0.56	< 0.0001	1.76 (1.36 to 2.27)
DM * Cohort 2	-0.26	0.01	0.78 (0.61 to 0.94)

[a] in calculating hazard ratio, reference group for cohort 2 is Cohort 1, for age is 20–39 year-old, for gender is female, for comorbidity index is comorbidity index = 0. The reference group for DM, HTN, history of coronary artery bypass graft (CABG) and history of congestive heart failure (CHF) were non-DM, non-HTN, no CABG and no CHF.

A more clinical-concerned inquiry may be why PD patients with DM respond to the increase in erythropoietin dosage and Hct levels more sensibly in terms of reducing cardiovascular risk. Definitely, our data do not allow us to test this clinical issue and thus more research to this end seems warranted. There are limitations of this study. No blood pressure or laboratory data including serum albumin, lipid profile was available in NHI claim database which limit us for a comprehensive comparison of baseline characteristics in these two cohorts. Although this might constrain detailed matching of patients in two cohorts, the patients matched in two cohorts were considerably comparable from the comparisons of comorbid conditions and concomitant medication related to cardiovascular risk.

5. Conclusions

While the findings demonstrating that pushing Hct to more than 36% compared to 30–36% tend to increase cardiovascular risk [1–3, 7] have been widely accepted and recommended, lack of sufficient evidences to present whether there exist differences in cardiovascular risk by maintaining Hct levels below 30% relative to 30–36%. Our study provided a natural experiment to answer this question. Matched Cohort 1 and Cohort 2 had comparable baseline characteristics. This suggests that both cohorts had

similar cardiovascular risk factors. After loosening erythropoietin payment criteria, significant lower risk of cardiovascular events, stroke and heart failure hospitalization was observed in matched Cohort 2, in particular those with diabetes mellitus. The risk reduction may be related to higher erythropoietin dosage and adequate Hct range. Further research is needed to investigate why PD patients with DM are more sensible to the increase in erythropoietin dosage and Hct levels. Our findings support that, for PD patients with DM, maintaining a Hct level higher than 30% is crucial for reducing cardiovascular risk. This provides implication for policy makers how to use healthcare resources cost-effectively while reducing potential cardiovascular risk for PD patients.

Declarations

Ethics Approval and Consent to Participate

The study has been approved by the ethical review board of National Taiwan University Hospital (NTUH-REC No.201406018W). Informed consent was not obtained from the study participants because the data was analyzed anonymously and was in accordance with Institutional Review Board guidelines. The Institutional Review Board has verified the anonymity of data analysis performed in this study.

Consent for Publication

All authors consent to the publication of this final version of manuscript.

Availability of Data and Material

Original data will be available upon request.

Competing Interests

The authors declare that the research was conducted in the absence of any commercial or financial competing interests. The listed authors also declare not to have both financial and non-financial interests. The results presented in this paper have not been published previously in whole or part.

Funding

This work was partly supported by a grant from the National Science Council of Taiwan (NSC99-2410-H-002-008).

Authors' Contributions

This work is based in part on the data from the National Health Insurance Research Database provided by National Health Insurance Administration, Ministry of Health and Welfare and managed by National Health Research Institutes. The views are solely those of the authors and do not represent those of the National Health Insurance Administration, Ministry of Health and Welfare or National Health Research Institutes.

My co-authors have all contributed to this manuscript and approve of this submission. **Dr. Lai IC** contributed the conception and design of the study, data interpretation, drafting the article and with final approval of the version to be published. **Prof. Chang RE** contributed to the conception and design of the study, acquisition and interpretation of data, article revision and with final approval of the version to be published. **Prof. Hou YH** contributed to analysis and interpretation of data, revision article and with final approval of the version to be published. **Mr. Shih-Pi Lin** contributed to analysis and interpretation of data, drafting article and with final approval the version to be published. **Dr. Yang FJ and Dr. Wan T T.H.** contributed to analysis and interpretation of data, article revision and with final approval of the version to be published.

Acknowledgements

The authors would like to thank Mr. Shin-hung Meng for data management and Dr. Ya-Chi Wu for excellent statistical support.

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