

中文題目:低血糖增加末期腎衰竭透析患者死亡風險:台灣世代研究

英文題目: Hypoglycemia episodes predict long term mortality in end stage renal disease dialysis patients: Taiwan national cohort study

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## Abstract

**Background:** The relationship between previous hypoglycemia and mortality after dialysis in the diabetic end stage renal disease (ESRD) dialysis patients remains unclear. The aim of this study was to investigate whether hypoglycemia in pre-ESRD stage increase the risk of subsequent mortality after the initiation of dialysis.

**Methods:** This longitudinal cohort study examined the medical claims in the Taiwan National Health Insurance Research Database of diabetic ESRD patients who initiated dialysis between 2002 and 2006. Hypoglycemia was identified from the 3 years period before the first dialysis. The patients were followed until death, end of dialysis, or 31 December 2008. Mortality after the initiation of dialysis was collected. The cumulative proportion of survivors after the initiation of dialysis was calculated using Kaplan-Meier methods. Cox proportional hazards models were used to identify the risk factors of mortality after initiation of dialysis.

**Results:** We enrolled 21,000 adult incident diabetic ESRD dialysis patients. 4,493 patients (21.40%) had hypoglycemia during the 3-year pre-dialysis period. The patients with hypoglycemia were older and had more comorbidities than those without hypoglycemia (Table 1). During the follow-up period ( $3.2 \pm 1.7$  years), 9,505 (45.3%) of all dialysis patients died. Those who had hypoglycemia episodes had a 25 percent greater mortality risk (HR: 1.25, 95% CI: 1.19-1.31) (Table 2). Patients with no identified hypoglycemia episodes had 1-, 3-, and 6-year cumulative survival rates of 90.3%, 68.1% and 43.1%; those with one episode 87.4%, 61.6%, and 34.9%; and those with two or more 85.3%, 64.7%, and 28.3% (log-rank test:  $P < 0.001$ ) (Figure 1). Multivariate adjustment revealed the greater the number of hypoglycemia episodes, the higher the mortality rate (Table 3).

**Conclusion:** Hypoglycemia in diabetic pre-dialysis ESRD patients predicted subsequent long-term mortality after dialysis, the greater the number of episodes, the higher the risk of death. Glycemic management to avoid hypoglycemia is important in diabetic ESRD patients, especially those with comorbidities. Further studies need to investigate the mechanism between hypoglycemia and mortality in diabetic ESRD patients.

**Table 1. The characteristics of diabetic end-stage renal disease dialysis patients with (n = 4,493) and without (n =16,507) hypoglycaemic episodes during the 3-year period leading up to initiation of dialysis.**

|                                  | Without Hypoglycemia<br>(n= 16,507) |        | With Hypoglycemia<br>(n= 4,493) |        | P      |
|----------------------------------|-------------------------------------|--------|---------------------------------|--------|--------|
|                                  | n                                   | (%)    | n                               | (%)    |        |
| Sex                              |                                     |        |                                 |        | <0.001 |
| Female                           | 8058                                | (77.0) | 2407                            | (23.0) |        |
| Male                             | 8449                                | (80.2) | 2086                            | (19.8) |        |
| Age (years)                      |                                     |        |                                 |        | 0.015  |
| 18-44                            | 1094                                | (81.5) | 248                             | (18.5) |        |
| 45-64                            | 7912                                | (78.7) | 2139                            | (21.3) |        |
| ≥ 65                             | 7501                                | (78.1) | 2106                            | (21.9) |        |
| Congestive heart failure         |                                     |        |                                 |        | <0.001 |
| No                               | 9992                                | (81.1) | 2336                            | (18.9) |        |
| Yes                              | 6515                                | (75.1) | 2157                            | (24.9) |        |
| Coronary artery disease          |                                     |        |                                 |        | <0.001 |
| No                               | 9751                                | (80.0) | 2444                            | (20.0) |        |
| Yes                              | 6756                                | (76.7) | 2049                            | (23.3) |        |
| Cerebrovascular disease          |                                     |        |                                 |        | <0.001 |
| No                               | 12450                               | (80.5) | 3019                            | (19.5) |        |
| Yes                              | 4057                                | (73.4) | 1474                            | (26.6) |        |
| Dysrhythmia                      |                                     |        |                                 |        | 0.013  |
| No                               | 14773                               | (78.8) | 3963                            | (21.2) |        |
| Yes                              | 1734                                | (76.6) | 530                             | (23.4) |        |
| Other cardiac <sup>a</sup>       |                                     |        |                                 |        | 0.024  |
| No                               | 14043                               | (78.9) | 3761                            | (21.1) |        |
| Yes                              | 2464                                | (77.1) | 732                             | (22.9) |        |
| Peripheral vascular disease      |                                     |        |                                 |        | <0.001 |
| No                               | 15083                               | (79.3) | 3938                            | (20.7) |        |
| Yes                              | 1424                                | (72.0) | 555                             | (28.0) |        |
| Chronic obstructive lung disease |                                     |        |                                 |        | <0.001 |
| No                               | 13632                               | (79.4) | 3533                            | (20.6) |        |
| Yes                              | 2875                                | (75.0) | 960                             | (25.0) |        |

|                           |       |        |      |        |        |
|---------------------------|-------|--------|------|--------|--------|
| Gastrointestinal bleeding |       |        |      |        | <0.001 |
| No                        | 10596 | (79.9) | 2660 | (20.1) |        |
| Yes                       | 5911  | (76.3) | 1833 | (23.7) |        |
| Liver disease             |       |        |      |        | 0.018  |
| No                        | 14065 | (78.9) | 3764 | (21.1) |        |
| Yes                       | 2442  | (77.0) | 729  | (23.0) |        |
| Cancer                    |       |        |      |        | 0.001  |
| No                        | 15331 | (78.3) | 4239 | (21.7) |        |
| Yes                       | 1176  | (82.2) | 254  | (17.8) |        |

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<sup>a</sup>Includes pericarditis, endocarditis, myocarditis, other complications of heart disease, heart transplant, heart valve replacement, and cardiac devices.

**Table 2. Risk factor for all-cause mortality in diabetic end-stage renal disease dialysis patients (n = 21,000)**

| Covariate                                   | Univariate analysis | Multivariate analysis    |
|---|---------------------|--------------------------|
|   | HR (95% CI)         | HR (95% CI) <sup>b</sup> |
| Sex (Male v Female)                         | 0.97 (0.93-1.01)*   | 1.08 (1.03-1.12)*        |
| Age at initiation of Dialysis               |                     |                          |
| 18-44 (Reference)                           | 1                   | 1                        |
| 45-64                                       | 1.56 (1.40-1.75)*   | 1.41 (1.27-1.58)*        |
| ≥ 65  | 2.91 (2.61-3.24)*   | 2.43 (2.18-2.72)*        |
| Hypoglycemia (yes v no)                     | 1.32 (1.26-1.38)*   | 1.25 (1.19-1.31)*        |
| Congestive Heart Failure (yes v no)         | 1.42 (1.36-1.47)*   | 1.22 (1.17-1.27)*        |
| Coronary Artery Disease (yes v no)          | 1.37 (1.32-1.43)*   | 1.09 (1.04-1.13)*        |
| Cerebrovascular disease (yes v no)          | 1.51 (1.45-1.58)*   | 1.32 (1.26-1.38)*        |
| Peripheral Vascular Disease (yes v no)      | 1.27 (1.19-1.36)*   | 1.11 (1.04-1.18)*        |
| Dysrhythmia (yes v no)                      | 1.52 (1.43-1.61)*   | 1.17 (1.10-1.24)*        |
| Other cardiac <sup>a</sup> (yes v no)       | 1.21 (1.15-1.27)*   | 1.03 (0.98-1.09)         |
| Chronic obstructive lung disease (yes v no) | 1.37 (1.31-1.44)*   | 1.11 (1.05-1.17)*        |
| Liver disease (yes v no)                    | 1.28 (1.21-1.35)*   | 1.26 (1.19-1.33)*        |
| Gastrointestinal bleeding (yes v no)        | 1.26 (1.21-1.32)*   | 1.09 (1.04-1.14)*        |
| Cancer (yes v no)                           | 1.53 (1.42-1.65)*   | 1.35 (1.26-1.46)*        |

<sup>a</sup>Includes pericarditis, endocarditis, myocarditis, other complications of heart disease, heart transplant, heart valve replacement, and cardiac devices.

<sup>b</sup>HR adjusted for sex, age, hypoglycemia, congestive heart failure, coronary artery disease, cerebrovascular accident, peripheral vascular disease, other cardiac disease, dysrhythmia, chronic obstructive pulmonary disease, gastrointestinal bleeding, liver disease and cancer.

\* $P < 0.05$ .

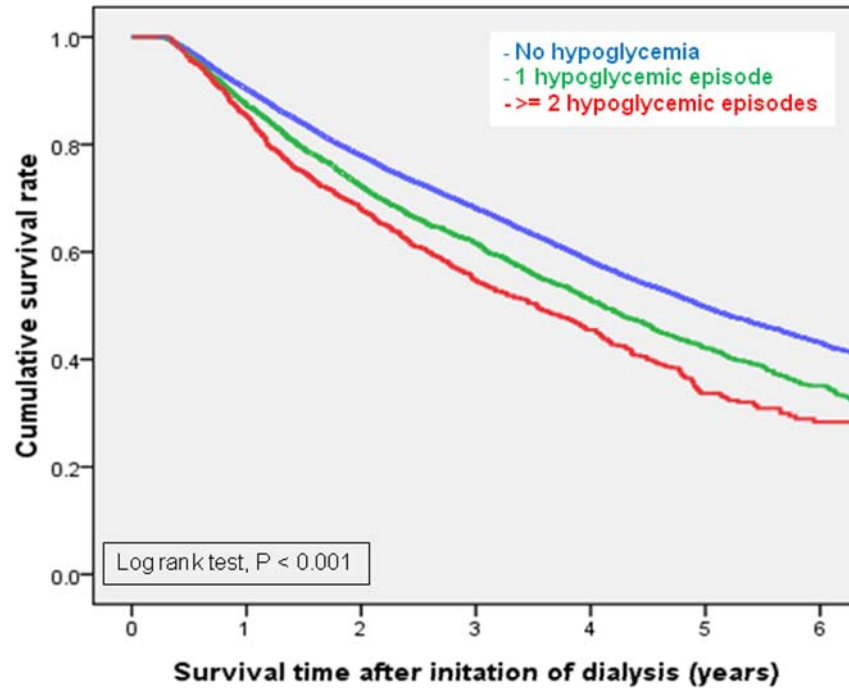
**Table 3. Incidence rate and risk factor for all-cause mortality by hypoglycaemic status**

| Hypoglycaemic episodes | Without death | With death   | Mean survival rate (year) | Univariate analysis | Multivariate analysis |
|------------------------|---------------|--------------|---------------------------|---------------------|-----------------------|
|                        | (n= 11495)    | (n= 9505)    |                           | Rate (95%)          | HR (95% CI)           |
| No                     | 9313 (56.4%)  | 7194 (43.6%) | 4.57 (4.53-4.61)          | Reference           | Reference             |
| 1                      | 1666 (50.0%)  | 1668 (50.0%) | 4.15 (4.06-4.24)          | 1.26 (1.19-1.33)*   | 1.20 (1.14-1.27)*     |
| ≥2                     | 516 (44.5%)   | 643 (55.5%)  | 3.80 (3.64-3.96)          | 1.51 (1.40-1.64)*   | 1.34 (1.26-1.49)*     |

<sup>a</sup>HR adjusted for sex, age, hypoglycemia, congestive heart failure, coronary artery disease, cerebrovascular accident, peripheral vascular disease, other cardiac disease, dysrhythmia, chronic obstructive pulmonary disease, gastrointestinal bleeding, liver disease and cancer.

\* $P < 0.05$ .

**Figure 1. Overall survival curves after initiation of dialysis stratified by hypoglycaemic status during the 3-year period leading up to initiation of dialysis: without hypoglycaemic episode (n =16,507), with one hypoglycaemic episodes(n = 3,334) and with 2 or more hypoglycaemic episodes (n = 1,159).**



| Number at risk             |       | Survival time after initiation of dialysis (years) |       |      |      |      |      |   |
|----------------------------|-------|--|-------|------|------|------|------|---|
|                            |       | 0  | 1     | 2    | 3    | 4    | 5    | 6 |
| No hypoglycemia group      | 16507 | 14834  | 12741 | 8680 | 5300 | 2973 | 1322 |   |
| 1 hypoglycemic episode     | 3334  | 2902   | 2397  | 1537 | 898  | 468  | 192  |   |
| >= 2 hypoglycemic episodes | 1159  | 988  | 787   | 474  | 269  | 119  | 48   |   |