EBM

Reporter: Intern 林惠甄
Supervisor: 紐聖文醫師
Date: 2012/11/02

CLINICAL SCENARIO

This 68 year-old female is a case of chronic kidney disease stage 5, hypertension.

In the past 16 years, she visited Nephrology OPD for her impaired renal function (GFR: 11, Lab data: BUN:63.4 , Cr:5.0). She denied other associated symptoms, such as general edema, formy urine, poor appetite, shortness of breath, dizziness.

She is worried about her quality of life would be affected by hemodialysis. Does initiation of hemodialysis be postponed?

.

CLINICAL QUESTION

Does late initiation of hemodialysis cause poor prognosis compared to early one?

EBM的步驟

Asking

- 將病人的問題寫成PICO

Acquire

- 找資料來回答問題

Appraisal

- 嚴格評讀文獻

Apply

- 是否可應用到病人身上

PICO

Patient/Problem	Advanced stage chronic kidney disease patients
Intervention	Early initiation of hemodialysis
Comparison	Late initiation of hemodialysis
Outcome	Mortality rate, morbidity rate or complication rate

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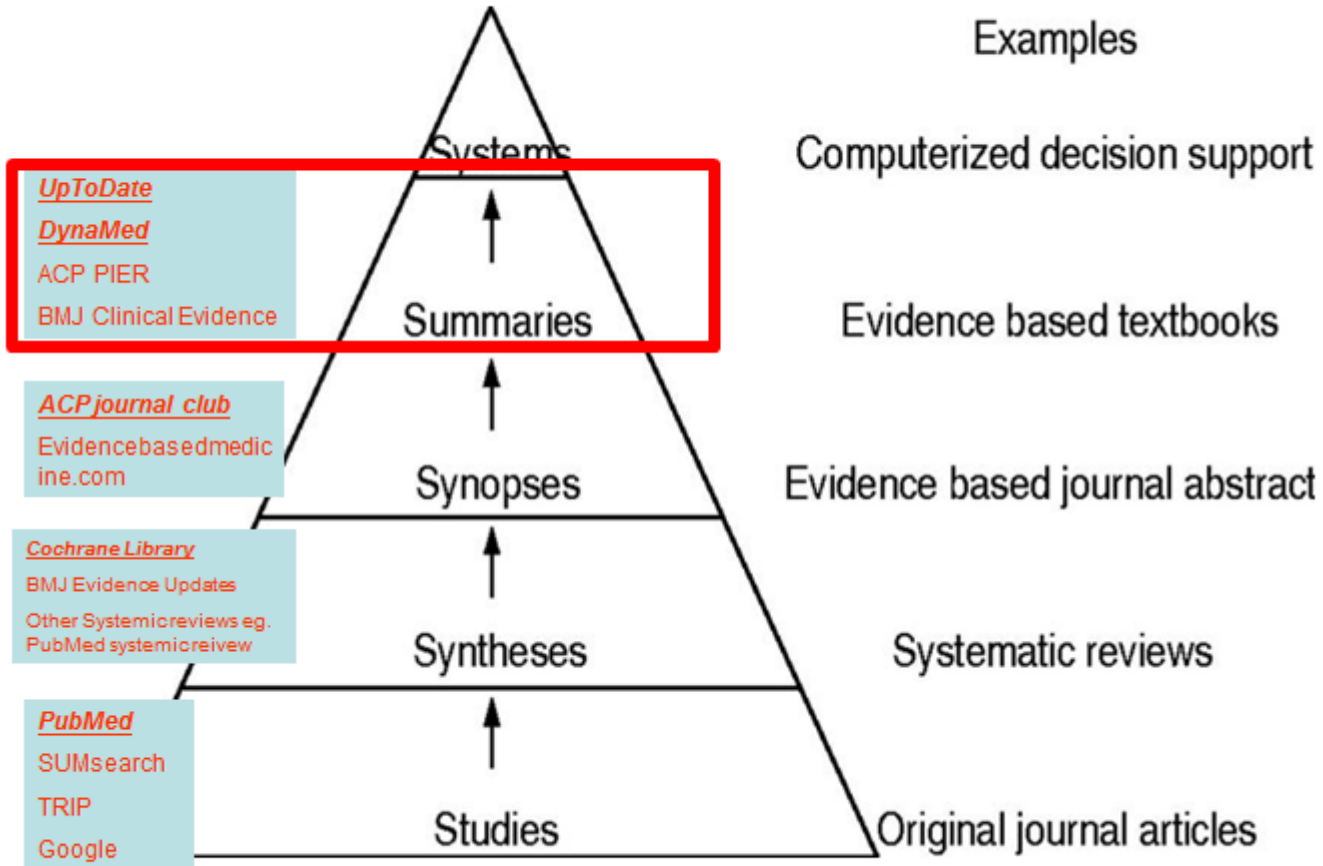
Search strategy: 5S model



Brian Haynes, R Evid Based Med 2006;11:162-164

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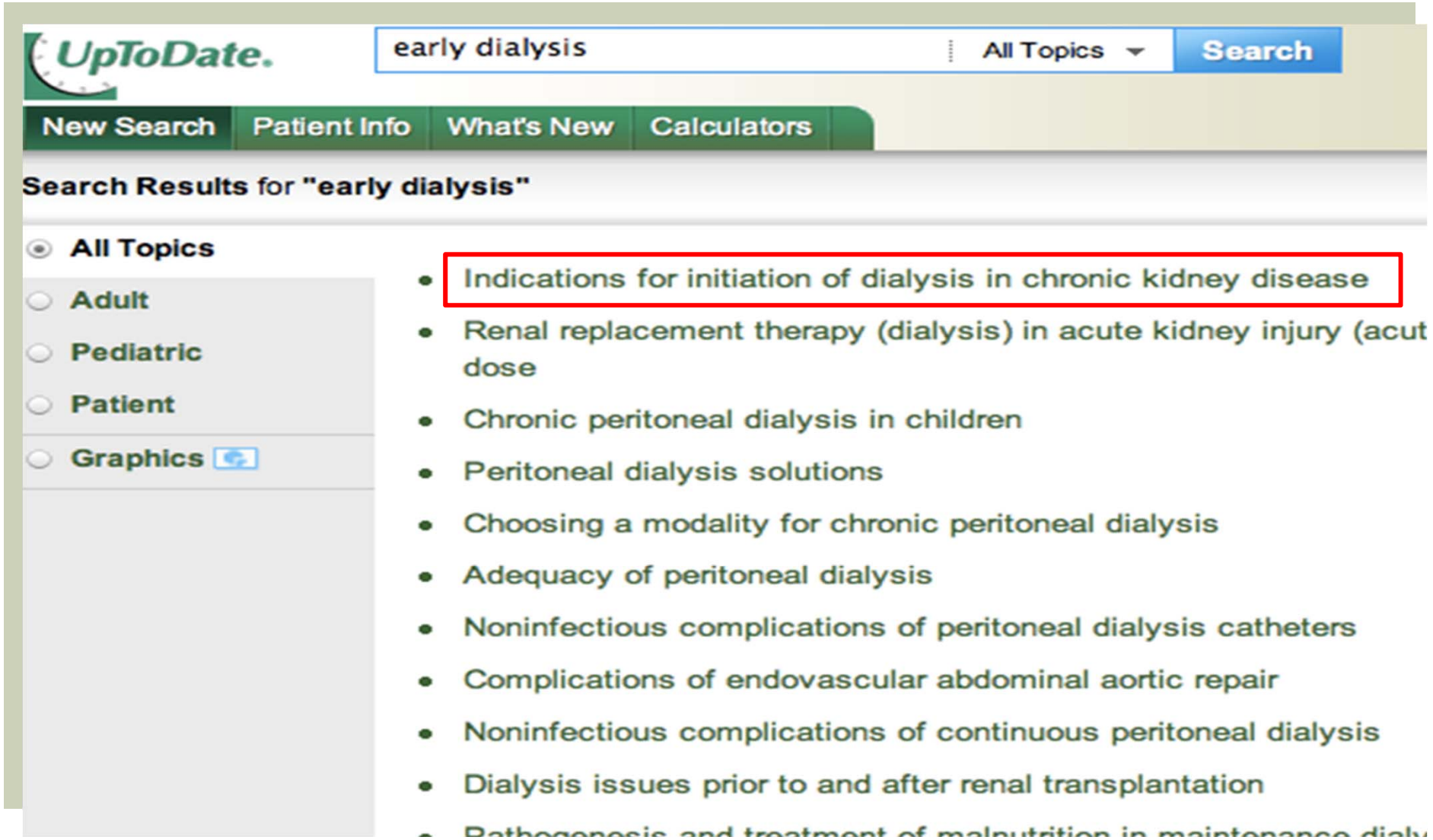
UPTODATE

Keyword: early dialysis, initiation of dialysi



UPTODATE

- A Randomized, Controlled Trial of Early versus Late Initiation of Dialysis (August 2012, NEJM)

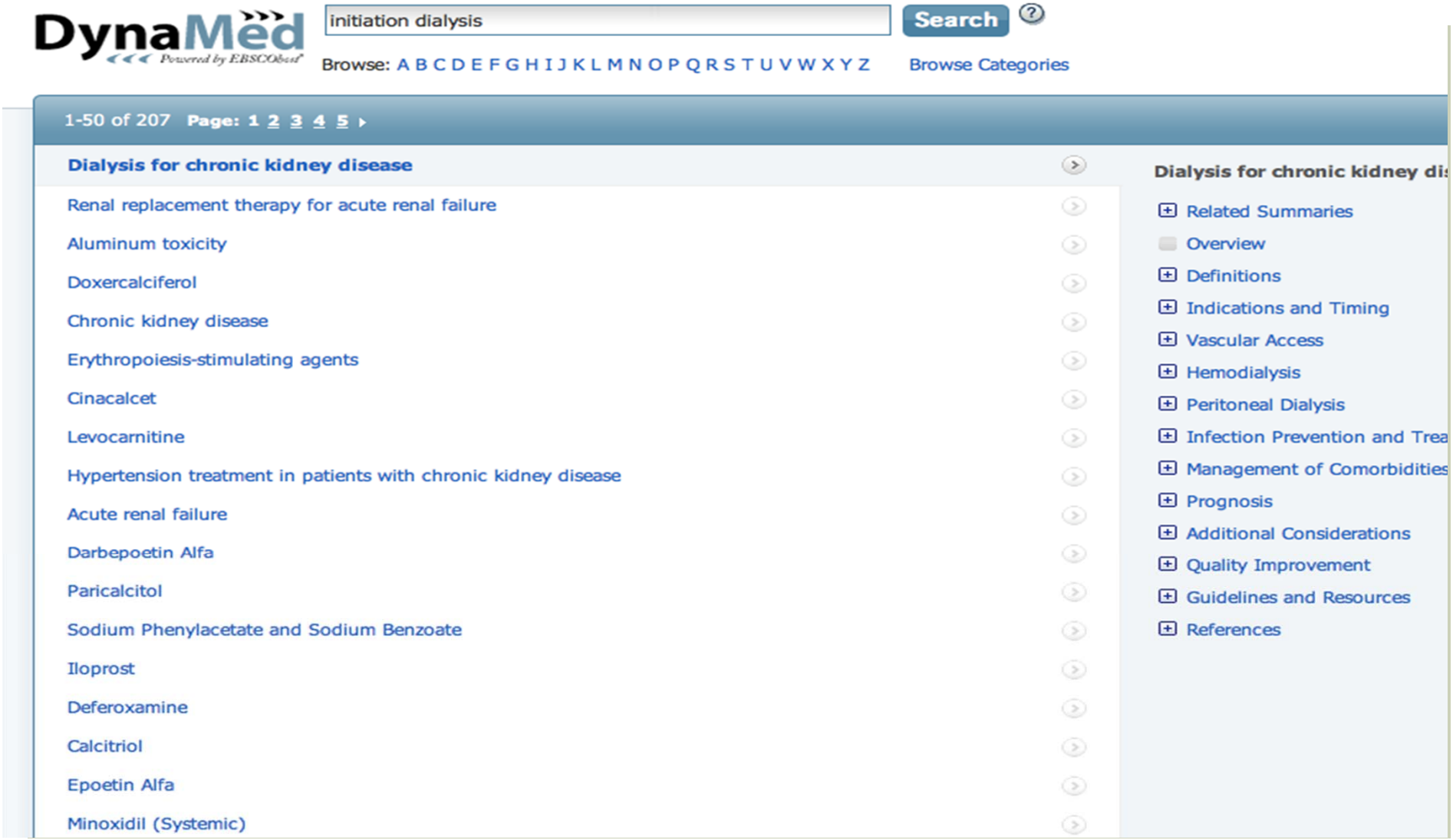
DOES EARLY DIALYSIS OR REFERRAL IMPROVE SURVIVAL/OUTCOMES?

Survival and dialysis complications — There is conflicting evidence concerning the effect of the early initiation of dialysis on survival. Some retrospective and uncontrolled prospective studies have reported a benefit associated with early initiation [19-22] whereas others have reported increased mortality [23-25].

The only randomized controlled trial that examined mortality and time of dialysis initiation, the IDEAL study, found no difference in survival between early or late initiation of dialysis. In this study, 828 patients with progressive CKD and an estimated GFR between 10 and 15 mL/min per 1.73 m2 (as determined by the Cockcroft-Gault equation) were randomly assigned to dialysis initiation when the estimated GFR was either 10 to 14 mL/min per 1.73 m2 or 5 to 7 mL/min per 1.73 m2 [26]. The median time to the initiation of dialysis was 1.8 and 7.4 months in the early and late start groups, respectively. At a median followup period of 3.6 years, the two groups had no significant difference in survival (38 and 37 percent mortality, hazard ratio of 1.05 with early initiation, 95% CI 0.83-1.30) as well as no difference in cardiovascular events, infections, or dialysis complications.

DYNAMED

Keyword: early dialysis
initiation of dialysis



DYNAMED

Keyword: early dialysis
initiation of dialysis

earlier initiation of dialysis does not appear to increase survival in patients with chronic kidney disease

- based on 1 randomized trial without blinding and 2 cohort studies

(level 2 [mid-level] evidence)

.A Randomized, Controlled Trial of Early versus Late Initiation of Dialysis (2010, NEJM)

.Association between estimated glomerular filtration rate at initiation of dialysis and
mortality (2011, CMAJ)

early start of dialysis associated with increased mortality in patients without diabetes or other comorbidities

- based on retrospective cohort study

(level 2 [mid-level] evidence)

.Association between estimated glomerular filtration rate at initiation of dialysis and
mortality (2011, CMAJ)

CMAJ

RESEARCH

Association between estimated glomerular filtration rate at initiation of dialysis and mortality

William F. Clark MD, Yingbo Na MSc, Steven J. Rosansky MD, Jessica M. Sontrop PhD, Jennifer J. Macnab PhD, Richard J. Glassock MD, Paul W. Eggers PhD, Kirby Jackson BSc, Louise Moist MD MSc

See related commentary by Stel and Jager, page 24

Abstract

Background: Recent studies have reported a trend toward earlier initiation of dialysis (i.e., at higher levels of glomerular filtration rate) and an association between early initiation and increased risk of death. We examined trends in initiation of hemodialysis within Canada and compared the risk of death between patients with early and late initiation of dialysis.

Methods: The analytic cohort consisted of 25 910 patients at least 18 years of age who initiated hemodialysis, as identified from the Canadian Organ Replacement Register (2001–2007). We defined the initiation of dialysis as early if the estimated glomerular filtration rate was greater than 10.5 mL/min per 1.73 m^2. We fitted time-dependent proportional-hazards Cox models to compare the risk of death between patients with early and late initiation of dialysis.

Results: Between 2001 and 2007, mean estimated glomerular filtration rate at initiation of dialysis increased from 9.3 (standard deviation [SD] 5.2) to 10.2 (SD 7.1) ($p < 0.001$), and the proportion of early starts rose from 28% (95% confidence interval [CI] 27%–30%) to 36% (95% CI 34%–37%). Mean glomerular filtration rate was 15.5 (SD 7.7) mL/min per 1.73 m^2 among those with early initiation and 7.1 (SD 2.0) mL/min per 1.73 m^2 among those with late initiation. The unadjusted hazard ratio (HR) for mortality with early relative to late initiation was 1.48 (95% CI 1.43–1.54). The HR decreased to 1.18 (95% CI 1.13–1.23) after adjustment for demographic characteristics, serum albumin, primary cause of end-stage renal disease, vascular access type, comorbidities, late referral and transplant status. The mortality differential between early and late initiation per 1000 patient-years narrowed after one year of follow-up, but never crossed and began widening again after 24 months of follow-up. The differences were significant at 6, 12, 30 and 36 months.

Interpretation: In Canada, dialysis is being initiated at increasingly higher levels of glomerular filtration rate. A higher glomerular filtration rate at initiation of dialysis is associated with an increased risk of death that is not fully explained by differences in baseline characteristics.

搜尋到的文章內容

ORIGINAL INVESTIGATION

ONLINE FIRST | LESS IS MORE

Early Start of Hemodialysis May Be Harmful

Steven J. Rosansky, MD; Paul Eggers, PhD; Kirby Jackson, BA; Richard Glassock, MD; William F. Clark, MD

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Background: A dramatic increase in the "early start" of dialysis with an estimated glomerular filtration rate (eGFR) at least 10 mL/min/1.73 m^2 has occurred in the United States since at least 1996. Several recent studies have reported a comorbidity-adjusted survival disadvantage of early start of dialysis. The current study examines a relatively "healthy" dialysis cohort to minimize confounding issues and determine whether early initiation of hemodialysis is associated with a survival benefit or harm.

Methods: We examined demographics, year of dialysis initiation, primary etiology of renal failure, and body mass index, hemoglobin, and serum albumin levels in 81 176 nondiabetic, 20- to 64-year-old, in-center incident hemodialysis patients with no reported comorbidity besides hypertension. We compared survival, using a piecewise proportional hazards model to estimate covariate-adjusted mortality hazard ratios (HRs) for eGFR at the time of initiation of dialysis. We also performed time-dependent adjusted analysis stratified by initial serum albumin levels lower than 2.5 g/dL, 2.5 to 3.49 g/dL, and 3.5 g/dL or higher (the "healthiest" group [HG]).

Results: Unadjusted 1-year mortality by eGFR ranged from 6.8% in the reference group (eGFR <5.0 mL/min/1.73 m^2) to 20.1% in the highest eGFR group (≥15.0 mL/min/1.73 m^2). Compared with the reference group, the HR for the HG was 1.27 (eGFR, 5.0-9.9 mL/min/1.73 m^2), 1.53 (eGFR, 10.0-14.9 mL/min/1.73 m^2), and 2.18 (eGFR ≥15.0 mL/min/1.73 m^2) and ranged from 1.50 to 3.53 mL/min/1.73 m^2 in the first year of dialysis for the early-start group.

Conclusion: The increased HR during hemodialysis associated with early start in the healthiest group of patients undergoing dialysis indicates that early start of dialysis may be harmful.

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A Randomized, Controlled Trial of Early versus Late Initiation of Dialysis

Bruce A. Cooper, M.B., B.S., Ph.D., Pauline Branley, B.Med., Ph.D., Liliana Bulfone, B.Pharm., M.B.A., John F. Collins, M.B., Ch.B., Jonathan C. Craig, M.B., Ch.B., Ph.D., Margaret B. Fraenkel, B.M., B.S., Ph.D., Anthony Harris, M.A., M.Sc., David W. Johnson, M.B., B.S., Ph.D., Joan Kesselhut, Jing Jing Li, B.Pharm., B.Com., Grant Luxton, M.B., B.S., Andrew Pilmore, B.Sc., David J. Tiller, M.B., B.S., David C. Harris, M.B., B.S., M.D., and Carol A. Pollock, M.B., B.S., Ph.D., for the IDEAL Study*

BACKGROUND

BACKGROUND

In clinical practice, there is considerable variation in the timing of the initiation of maintenance dialysis for patients with stage V chronic kidney disease, with a worldwide trend toward early initiation. In this study, conducted at 32 centers in Australia and New Zealand, we examined whether the timing of the initiation of maintenance dialysis influenced survival among patients with chronic kidney disease.

METHODS

METHODS

We randomly assigned patients 18 years of age or older with progressive chronic kidney disease and an estimated glomerular filtration rate (GFR) between 10.0 and 15.0 ml per minute per 1.73 m^2 of body-surface area (calculated with the use of the Cockcroft–Gault equation) to planned initiation of dialysis when the estimated GFR was 10.0 to 14.0 ml per minute (early start) or when the estimated GFR was 5.0 to 7.0 ml per minute (late start). The primary outcome was death from any cause.

RESULTS

RESULTS

Between July 2000 and November 2008, a total of 828 adults (mean age, 60.4 years; 542 men and 286 women; 355 with diabetes) underwent randomization, with a median time to the initiation of dialysis of 1.80 months (95% confidence interval [CI], 1.60 to 2.23) in the early-start group and 7.40 months (95% CI, 6.23 to 8.27) in the late-start group. A total of 75.9% of the patients in the late-start group initiated dialysis when the estimated GFR was above the target of 7.0 ml per minute, owing to the development of symptoms. During a median follow-up period of 3.59 years, 152 of 404 patients in the early-start group (37.6%) and 155 of 424 in the late-start group (36.6%) died (*hazard ratio with early initiation*, 1.04; 95% CI, 0.83 to 1.30; P=0.75). There was no significant difference between the groups in the frequency of adverse events (cardiovascular events, infections, or complications of dialysis).

CONCLUSIONS

CONCLUSIONS

In this study, planned early initiation of dialysis in patients with stage V chronic kidney disease was not associated with an improvement in survival or clinical outcomes.

EBM的步驟

Asking

- 將病人的問題寫成PICO

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- 是否可應用到病人身上

證據等級

(針對**pubmed**找到的那篇論文做評讀)

Level	**與[治療/預防/病因/危害]有關的文獻**
1a	用多篇RCT[註1]所做成的綜合性分析(SR[註2] of RCTs)
1b	單篇RCT(有較窄的信賴區間)
1c	All or none
2a	用多篇世代研究所做成的綜合性分析
2b	單篇cohort及低品質的RCT
2c	Outcome research / ecological studies
3a	SR of case-control studies
3b	Individual case-control studies
4	Case-series(poor quality :cohort / case-control studies)
5	沒有經過完整評讀醫學文獻的專家意見

Grades of Recommendation

A	consistent level 1 studies
B	consistent level 2 or 3 studies ***or*** extrapolations from level 1 studies
C	level 4 studies ***or*** extrapolations from level 2 or 3 studies
D	level 5 evidence ***or*** troublingly inconsistent or inconclusive studies of any level

AAMPECOT

Answer

Q:文獻試圖回答什麼問題?

Whether the timing of the initiation of maintenance dialysis influenced survival among patients with chronic kidney disease.

Q:是否回答我的問題？

是(本病人GFR: 11，因此可以根據文章結果比較進入透析的時間對生存率的影響)

CONCLUSIONS

In this study, planned early initiation of dialysis in patients with stage V chronic kidney disease was not associated with an improvement in survival or clinical outcomes.

本文獻研究設計是屬於那一類？

Randomized Controlled Trials

Method - patient

- Patients were recruited at 32 centers in Australia and New Zealand.
- Inclusion criteria:
  - Progressive chronic kidney disease (patients with a failing kidney transplant were eligible)
  - An estimated GFR between 10.0 and 15.0 ml per minute per 1.73 m2 of body-surface area.

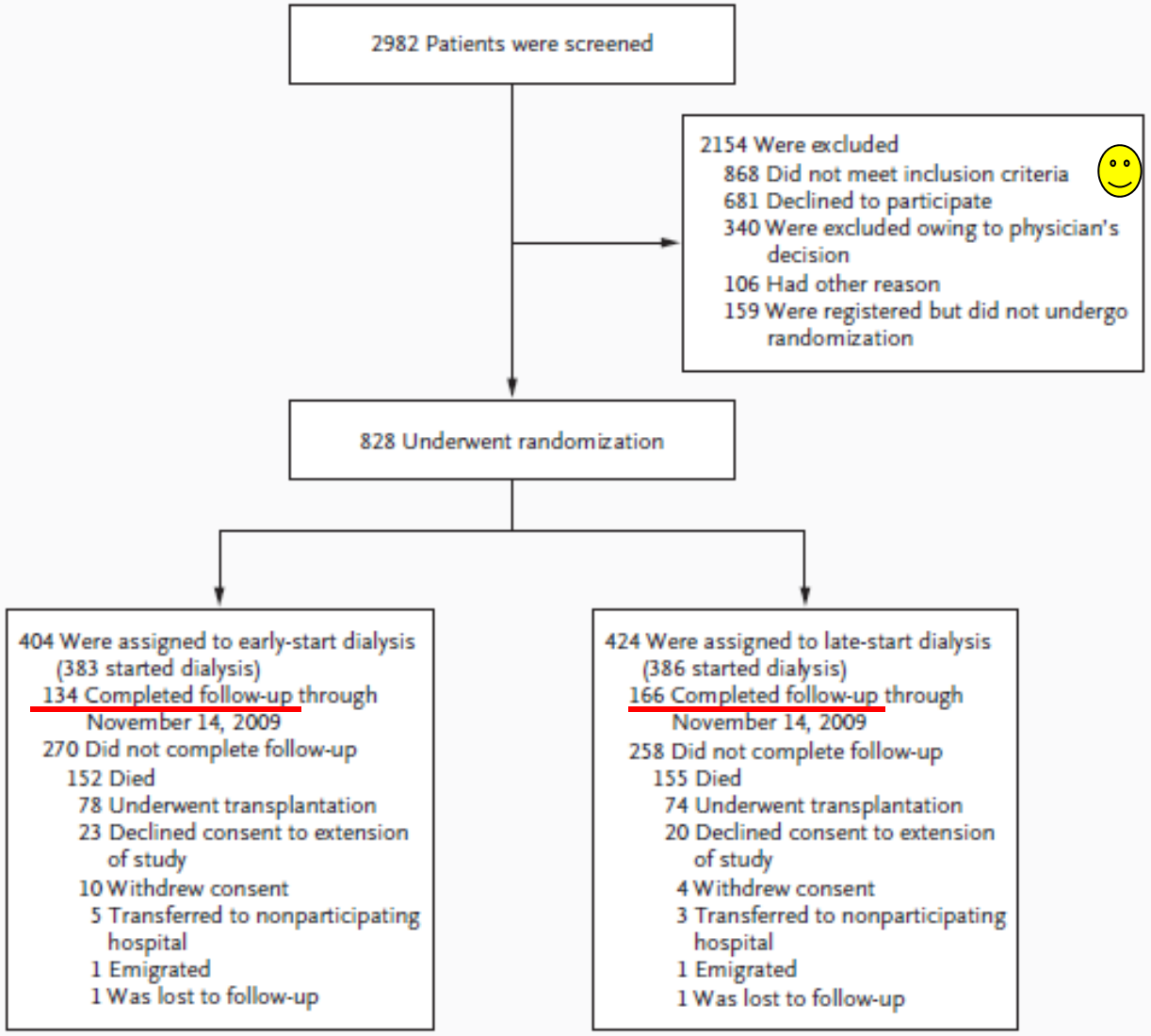

Figure 1. Enrollment, Randomization, and Follow-up.

The reasons that 159 patients were registered but did not undergo randomization are listed in Table 1 in the Supplementary Appendix. The reasons that patients randomly assigned to a group did not start dialysis were death (10 in the early-start group and 22 in the late-start group) and the following other reasons (11 in the early-start group and 16 in the late-start group): the GFR remained stable, the patient emigrated or transferred to a nonparticipating hospital, the patient withdrew consent, the patient underwent transplantation, or the patient could not be contacted. Patients could have more than one reason for not completing follow-up.

Study Treatment

- Early-start group
  - eGFR was 10.0 to 14.0 ml per minute
- late-start group
  - eGFR was 5.0 to 7.0 ml per minute
- The study protocol permitted patients who were assigned to the late-start group to commence dialysis when the estimated GFR was more than 7.0 ml per minute if the treating physician recommended that they do so.

Patient

Q:是否隨機取樣(randomization)? 是

Q:取樣是否具代表性(representative)?
是 (Intension to treat)

Table 1. Baseline Characteristics of the Patients.*

Variable	Early-Start Group (N = 404)	Late-Start Group (N = 424)
Sex (no.)		
Female	143	143
Male	261	281
Age (yr)	60.2±12.8	60.5±12.3
Time since first seen by nephrologist (mo)		
Median	32.5	29.4
Interquartile range	9.8–84.2	9.8–75
Race or ethnic group (%)†		
White	70.0	72.9
Asian	9.2	8.5
Maori	6.7	5.7
Pacific Islander	5.7	5.9
Aboriginal or Torres Strait Islander	3.2	2.1
Other‡	5.2	5.0
Primary cause of end-stage renal disease (%)		
Diabetes	33.9	34.0
Glomerulonephritis	16.1	17.2
Polycystic kidney disease	10.1	11.1

Hypertension	7.9	7.8
Analgesic nephropathy	4.7	4.0
Reflux nephropathy	4.7	3.3
Renovascular disease	3.7	5.4
Interstitial nephritis	2.2	0.9
Obstructive nephropathy	1.2	0.2
Failing kidney transplant	3.2	3.5
Other	15.3	16.0
Coexisting conditions (%)		
Diabetes	42.6	43.2
Hyperlipidemia	60.9	60.8
Cardiovascular disease	39.6	38.2
Ischemic heart disease	29.5	27.1
Peripheral vascular disease	17.1	18.6
Congestive heart failure	4.5	6.4
Stroke	2.7	2.1
Smoking status (%)		
Current smoker	11.4	11.1
Former smoker	50.7	47.2
Never smoked	37.9	41.8

Exposure
(Intervention Comparison)

Q:處置是否有清楚的描述(Ascertain)?是

Q:是否實際可行? 是

Outcome

Q:是否有客觀雙盲的測量(MBO)?否

Q:是否有統計學或臨床上的意義？

兩者無統計學上差異

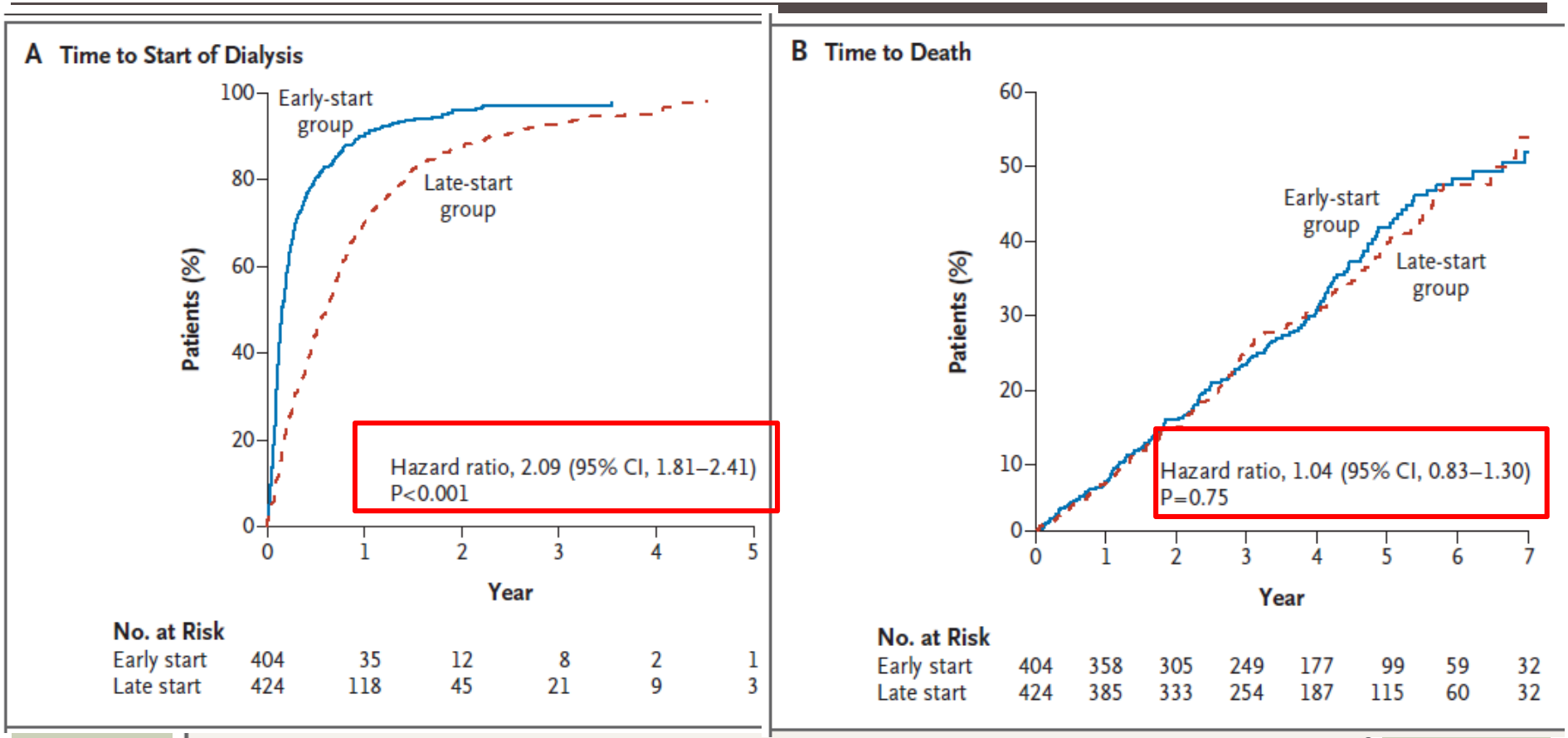

Figure 2. Kaplan–Meier Curves for Time to the Initiation of Dialysis and for Time to Death.

The data for time to the initiation of dialysis (Panel A) were censored at the time of death, transplantation, or withdrawal of consent or at the time a patient transferred to a nonparticipating hospital, emigrated, or could not be contacted. The curves for time to death (Panel B) are truncated at 7 years of follow-up and a cumulative hazard of 60%.

Subgroup	Early Start	Late Start	P Value for Interaction
	no. of deaths/no. of patients (%)		
GFR C–G			0.74
<12.5 ml/min/1.73 m^2	56/139 (40)	56/137 (41)	
≥12.5 ml/min/1.73 m^2	96/265 (36)	99/287 (34)	
GFR MDRD			0.58
<9.5 ml/min/1.73 m^2	58/195 (30)	57/203 (28)	
≥9.5 ml/min/1.73 m^2	94/209 (45)	98/221 (44)	
Age			0.26
<60 yr	39/180 (22)	38/194 (20)	
≥60 yr	113/224 (50)	117/230 (51)	
Sex			0.28
Female	55/143 (38)	58/143 (41)	
Male	97/261 (37)	97/281 (35)	
Diabetes			0.63
No	65/232 (28)	63/241 (26)	
Yes	87/172 (51)	92/183 (50)	
Body-mass index			0.59
<25.0	40/102 (39)	46/126 (37)	
25.0–29.9	53/143 (37)	52/146 (36)	
≥30.0	59/159 (37)	57/152 (38)	
Baseline history of cardiovascular disease			0.47
No	64/244 (26)	69/262 (26)	
Yes	88/160 (55)	86/162 (53)	
Albumin			0.67
<35 g/liter	38/68 (56)	44/81 (54)	
≥35 g/liter	110/325 (34)	109/336 (32)	

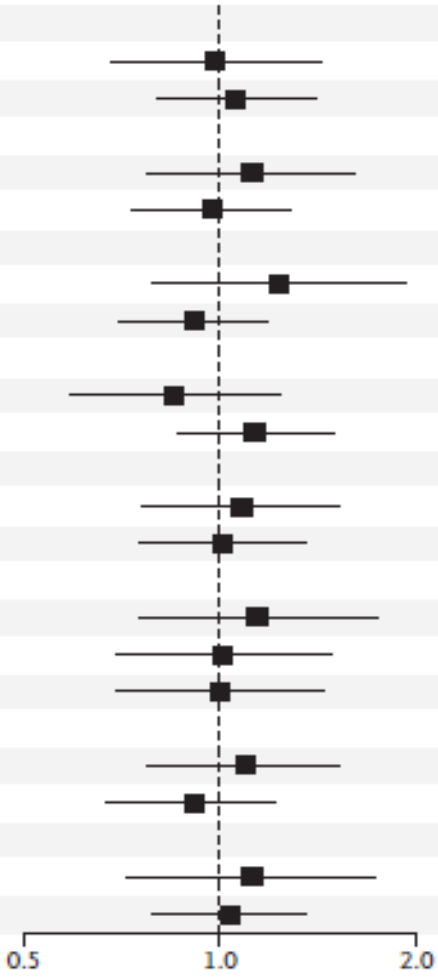

Figure 3. Effect of the Timing of Dialysis Initiation in Subgroups.

The forest plot shows the hazard ratio (and 95% confidence intervals) for the primary outcome of death from any cause, with early initiation as compared with late initiation of dialysis, according to each of the prespecified subgroups. The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters. GFR C–G denotes glomerular filtration rate estimated with the Cockcroft–Gault equation, and GFR MDRD the glomerular filtration rate estimated with the Modification of Diet in Renal Disease equation.

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Apply the Study to the Patient

早期透析跟晚期透析對於死亡率並不會帶來任何差異，
因此等病人症狀更明顯時再進入透析即可。

總結

Early and late initiation of dialysis did not differ for reduction of all-cause mortality in stage 5 chronic kidney disease.

THANK YOU FOR YOUR LISTENING

Method - exclusion

- Younger than 18 years of age
- An estimated GFR of less than 10.0 ml per minute
- Plans to receive a kidney transplant from a live donor within the next 12 months
- A recently diagnosed cancer that was likely to affect survival
- Unable to provide written informed consent