Mahidol University
Faculty of Medicine Ramathibodi Hospital
Department of Clinical Epidemiology and Biostatistics

Prognosis study

Atiporn Ingsathit, M.D., Ph.D. (Clin. Epid.)

Mahidol University
Faculty of Medicine Ramathibodi Hospital
Department of Clinical Epidemiology and Biostatistics

What is Evidence-Based Medicine (EBM) ?

"Expertise in integrating

1. Clinical Circumstance

2. Best research evidence

3. Patient values

in clinical decisions"

Haynes, Devereaux, & Guyatt, 2002

Mahidol University
Faculty of Medicine Ramathibodi Hospital
Department of Clinical Epidemiology and Biostatistics

Why we need EBM?

"helping smart doctors stop prescribing dumb treatments."

The 2009 Gairdner Awards for Medical Science lauded ***Dr. David Sackett*** *for his leadership in the fields of clinical epidemiology and evidence-based medicine.*

Mahidol University
Faculty of Medicine Ramathibodi Hospital
Department of Clinical Epidemiology and Biostatistics

How do we actually practice EBM?
5 A's of EBM

- Step 1: **A**sk answerable question
- Step 2: Find **A**rticles
- Step 3: Critical **A**ppraisal the evidence
- Step 4: **A**pply
- Step 5: **A**ssess

Type of question in clinical practice

- Diagnosis
- Etiology or causation
- Treatment
- **Prognosis**

Prognosis

- A prediction of the future course of disease following its onset.
  - A group of patients having something in common are assembled and followed forward in time, and clinical outcomes are measured.

“Natural history of disease”

  - The evolution of a disease that has come under treatment

“Clinical course”

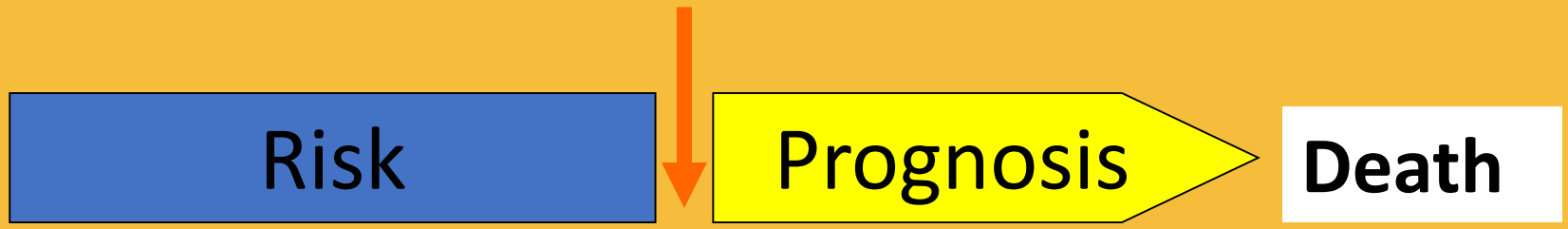
Why we measure prognosis?

- Clinicians require studies of prognosis to
  - Administering treatment
    - that does more good than harm
  - Counselling
    - Giving patients an indication of what the future is likely to hold
- Knowledge about prognosis can help clinicians make the right treatment decision.
  - Treatment options
  - Patient selection
  - Palliative care

Mahidol University
Faculty of Medicine Ramathibodi Hospital
Department of Clinical Epidemiology and Biostatistics

Risk vs. Prognosis

Onset of acute MI



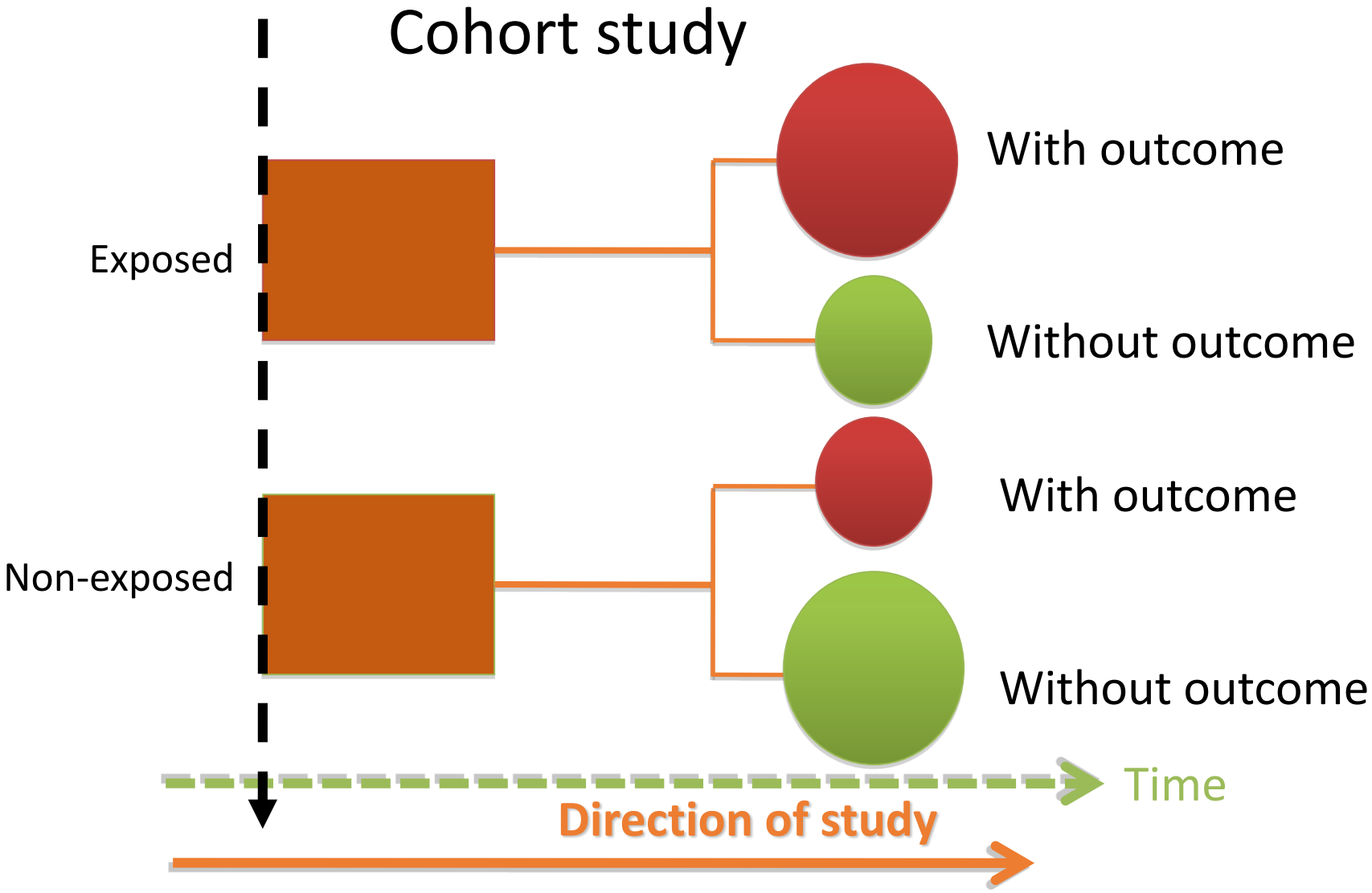
Risk factors
Age
Male
Smoking
HT
LDL
Inactivity

Prognostic factors
Age
Female
Smoking
Hypotension
Anterior infarction
CHF
Ventricular arrhythmia

Mahidol University
Faculty of Medicine Ramathibodi Hospital
Department of Clinical Epidemiology and Biostatistics

Risk vs. prognosis

Topic	Risk	Prognosis
Patient	Healthy people	Sick people
Outcome	Onset of disease	Consequences of disease - Disability - Complication - Death
Rate	Low-probability event 1/1000 to 1/100,000	Higher probability 20%-50%
Factor	Male had higher risk of AMI than female	Female will die after AMI than male
Study design	Cohort or case-control	Cohort


Cohort study
Exposed
Non-exposed
With outcome
Without outcome
With outcome
Without outcome
Time
Direction of study

How we measure prognosis?

- **Rates**
  - The proportion of people experiencing an event during a fixed time period
  - Follow 100 patients with rotaviral infection → 20 die → case fatality rate 20%
- **Survival analysis**
  - Survival probability
  - Hazard ratio

We may refine the prognosis by looking at subgroups defined by demographic variables. When these factors influences which patients do better or worse, we call them **prognostic factors**.

Rates commonly used to describe Prognosis

Rate	Definition
Case fatality	Percent of patients with a disease who die of it
Disease-specific mortality	Number of people per 100,000 population dying of a specific disease

Describing prognosis

- **Case-fatality rate**

  Percentage of people diagnosed as having a certain disease die within a certain time after diagnosis

$$\frac{\text{No. of individual dying during a specified period of time after disease onset}}{\text{No. of individuals with the specified disease}} \times 100$$

Describing prognosis

- **Case-fatality rate**

Example
A population of 100,000 people
20 are sick with disease X
18 die from disease X in one year

Disease-specific mortality rate = 18/100,000

= **0.018%**

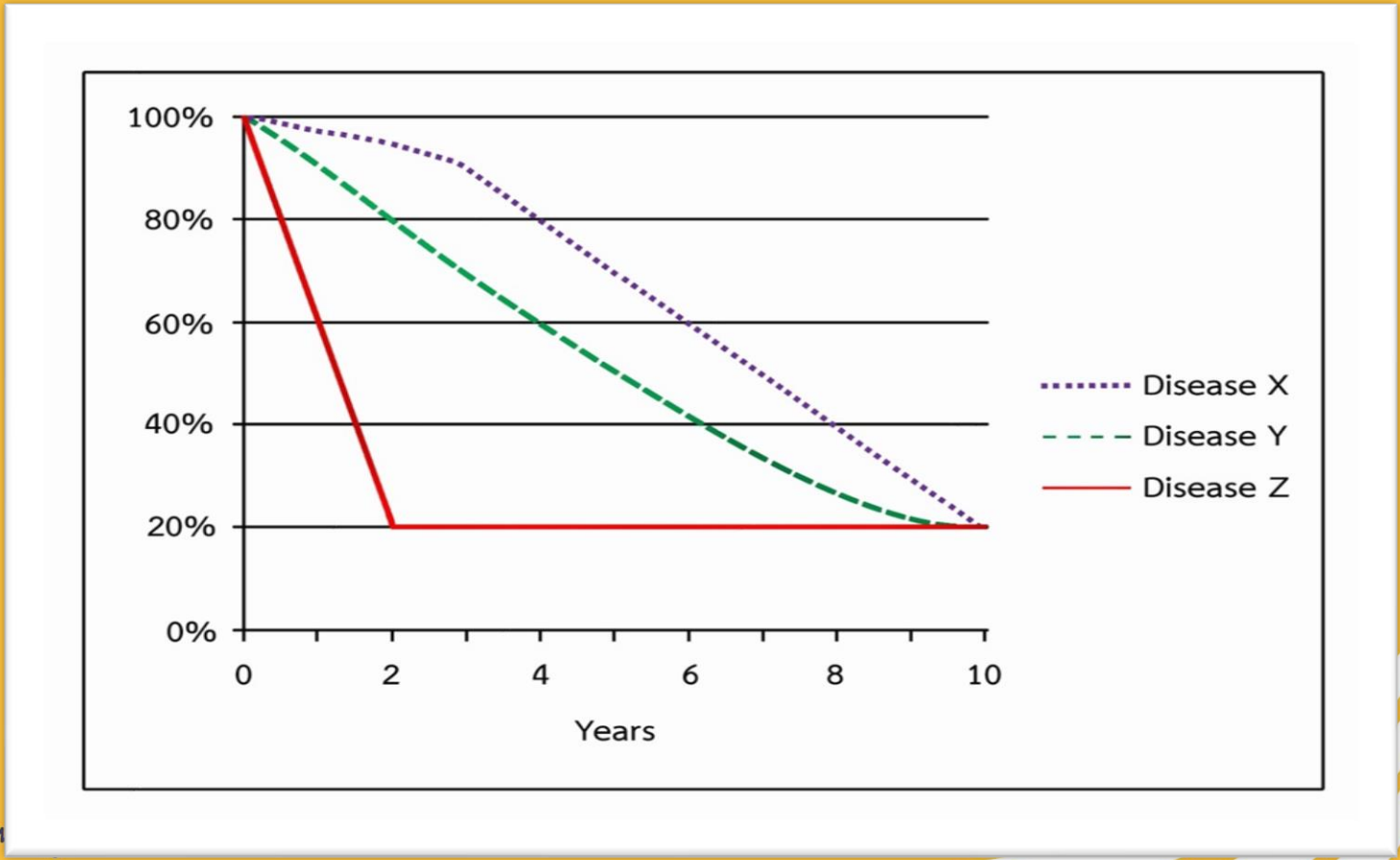
The case-fatality rate = 18/20 =**90%**

Rates commonly used to describe Prognosis

Rate	Definition
Case fatality	Percent of patients with a disease who die of it
Disease-specific mortality	Number of people per 100,000 population dying of a specific disease
Response	Percent of patients showing some evidence of improvement after intervention
Remission	Percent of patients entering a phase in which disease is no longer detectable
Recurrence	Percent of patients who have return of disease after a disease-free interval

Survival probability

- The figure below shows the survival curves for three diseases with the same survival rate at 10 years. Notice that the summary rate obscures important differences to patients.



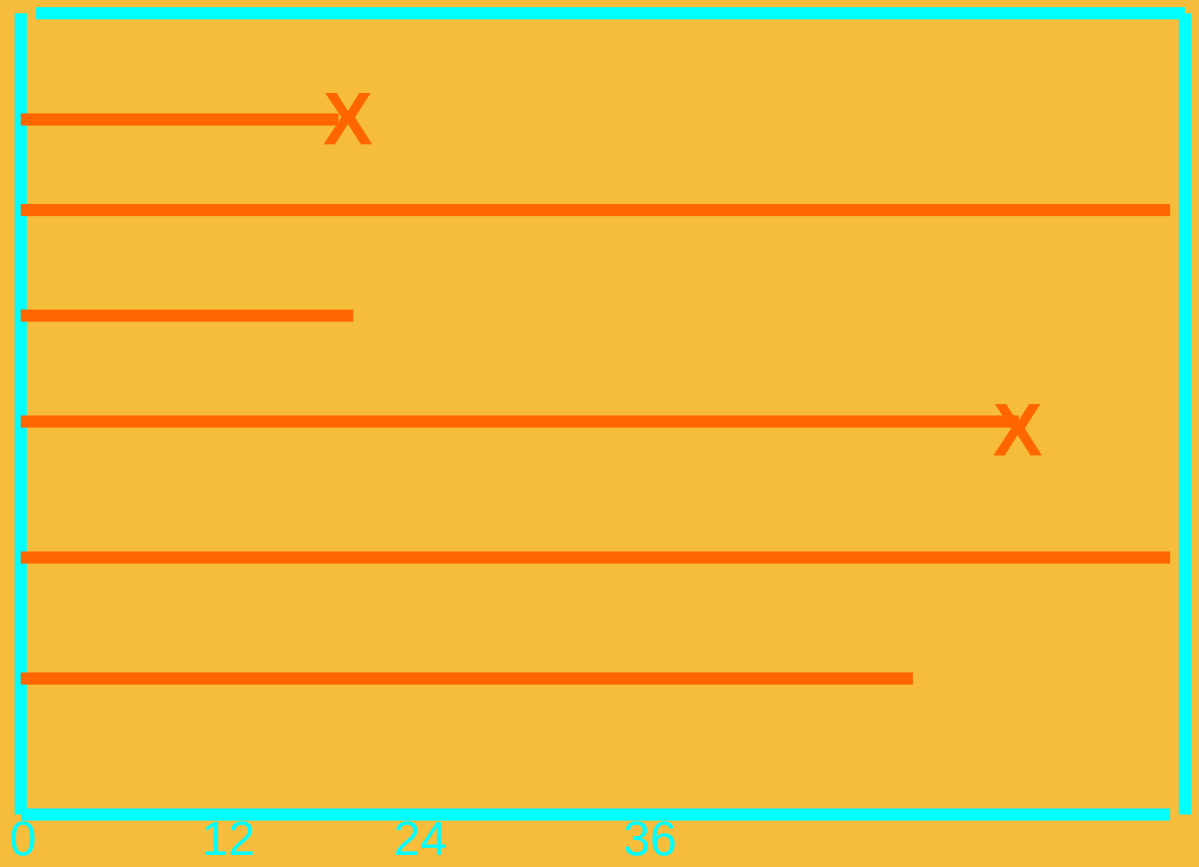
Mahidol University
Faculty of Medicine Ramathibodi Hospital
Department of Clinical Epidemiology and Biostatistics

Survival analysis

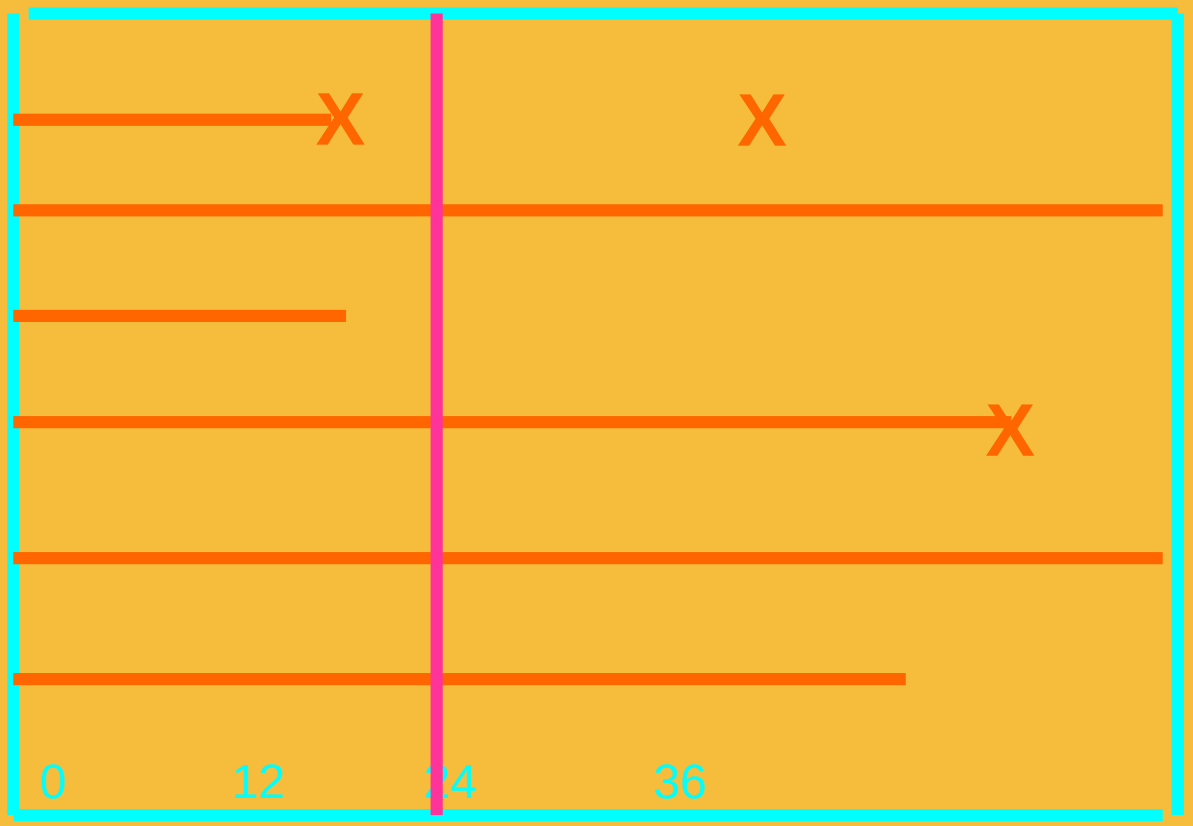
- The likelihood that patients with a given condition will experience an outcome at any point in time.
- Cohort or a randomized control trial
- Time to event

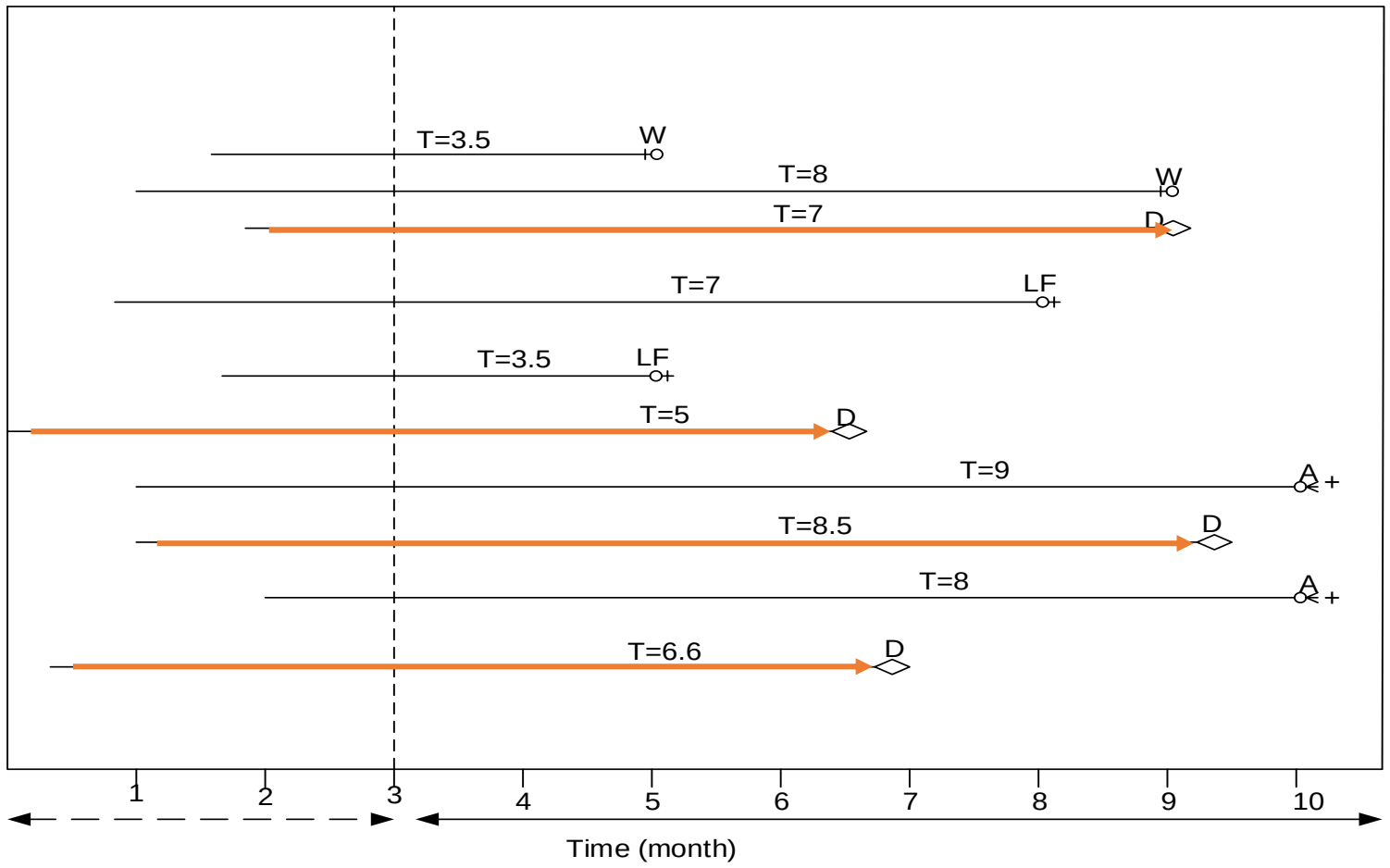
Origin → End point

- Censored: loss to follow-up or death
- Why?
  - The patients do not typically enter the study at the same time.
  - Investigators Frequently must analyze their data before all the subjects have died or the event has occurred.


X
X
0
12
24
36
Time (months)

Mortality rate: 1/6 = 0.16 or 1/5= 0.2





D=death, A=alive,
LF = lost follow-up, W=withdraw

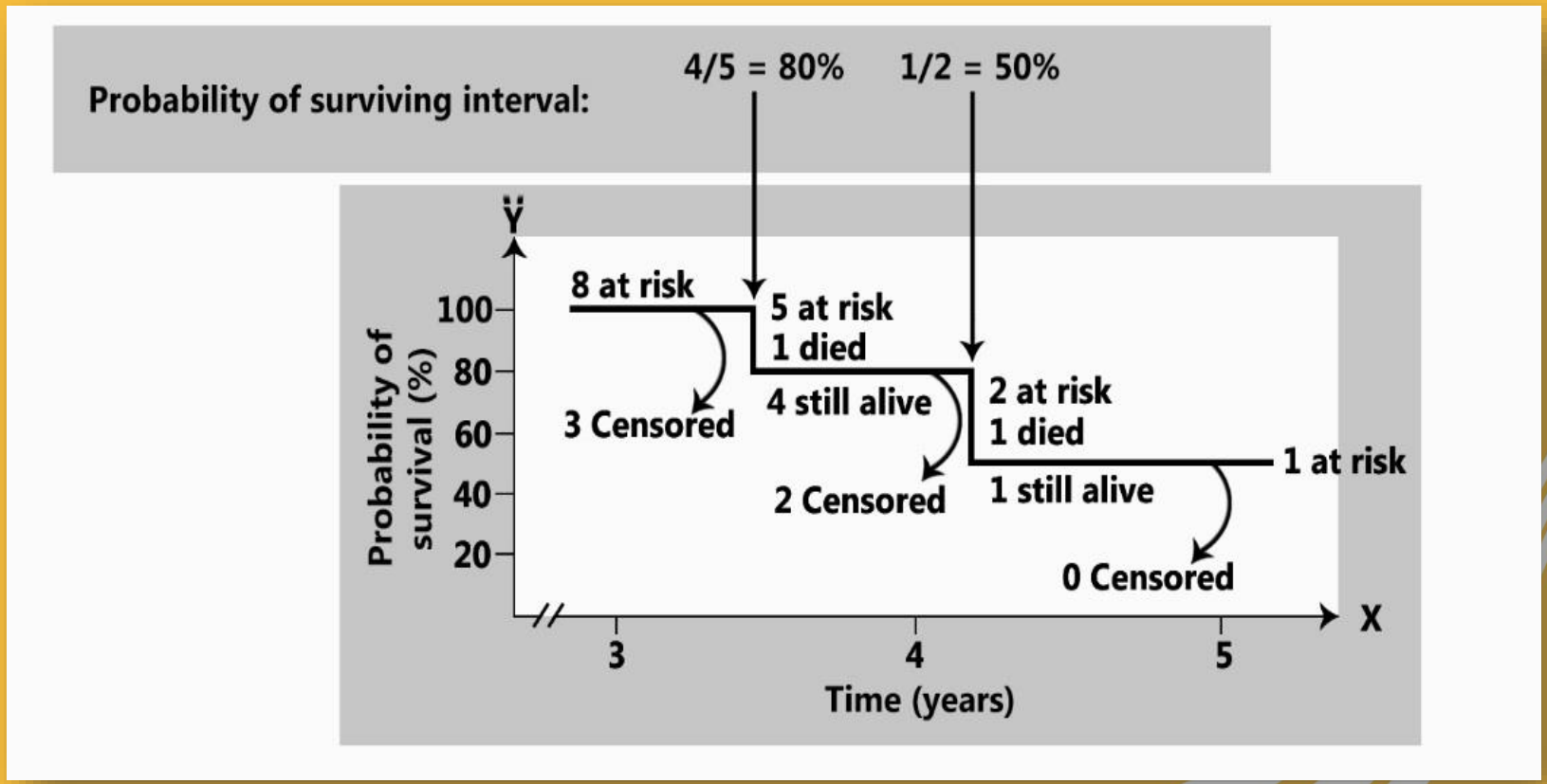
Total observed person-time 69.1 mo.

Methodological characteristics of survival study

- The starting date for each patient must clearly defined
  - date of diagnose
  - date of receiving treatment
  - date of operation, etc.
- The end date for each patient
- Patient's status at the end
  - Death if death is the final outcome
  - recurrence, disease free
  - infection, non-infection
  - remission, non-remission
  - recovery, non-recovery
  - loss to follow up, withdraw

Survival curve

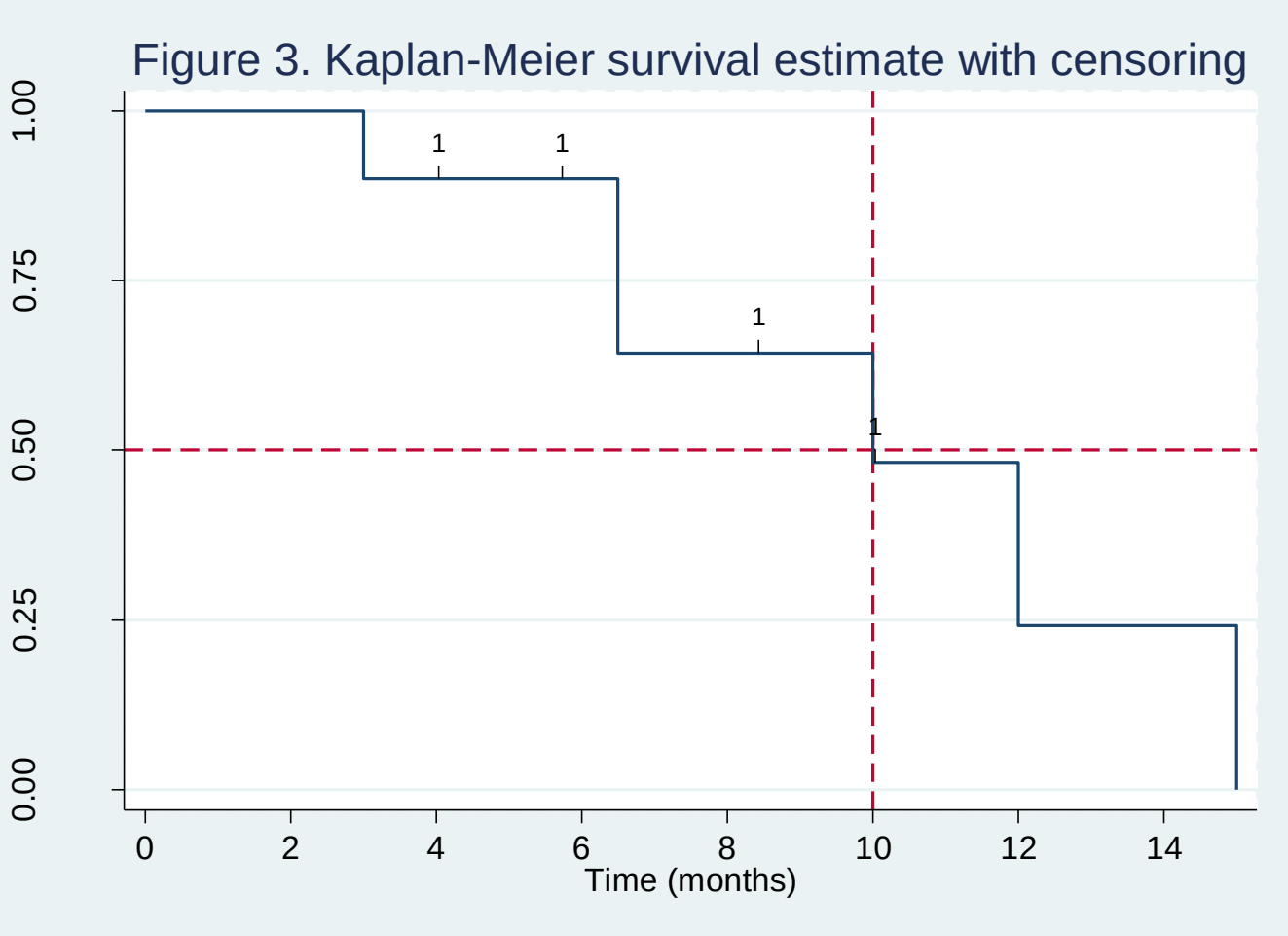
Simplify example of a survival curve



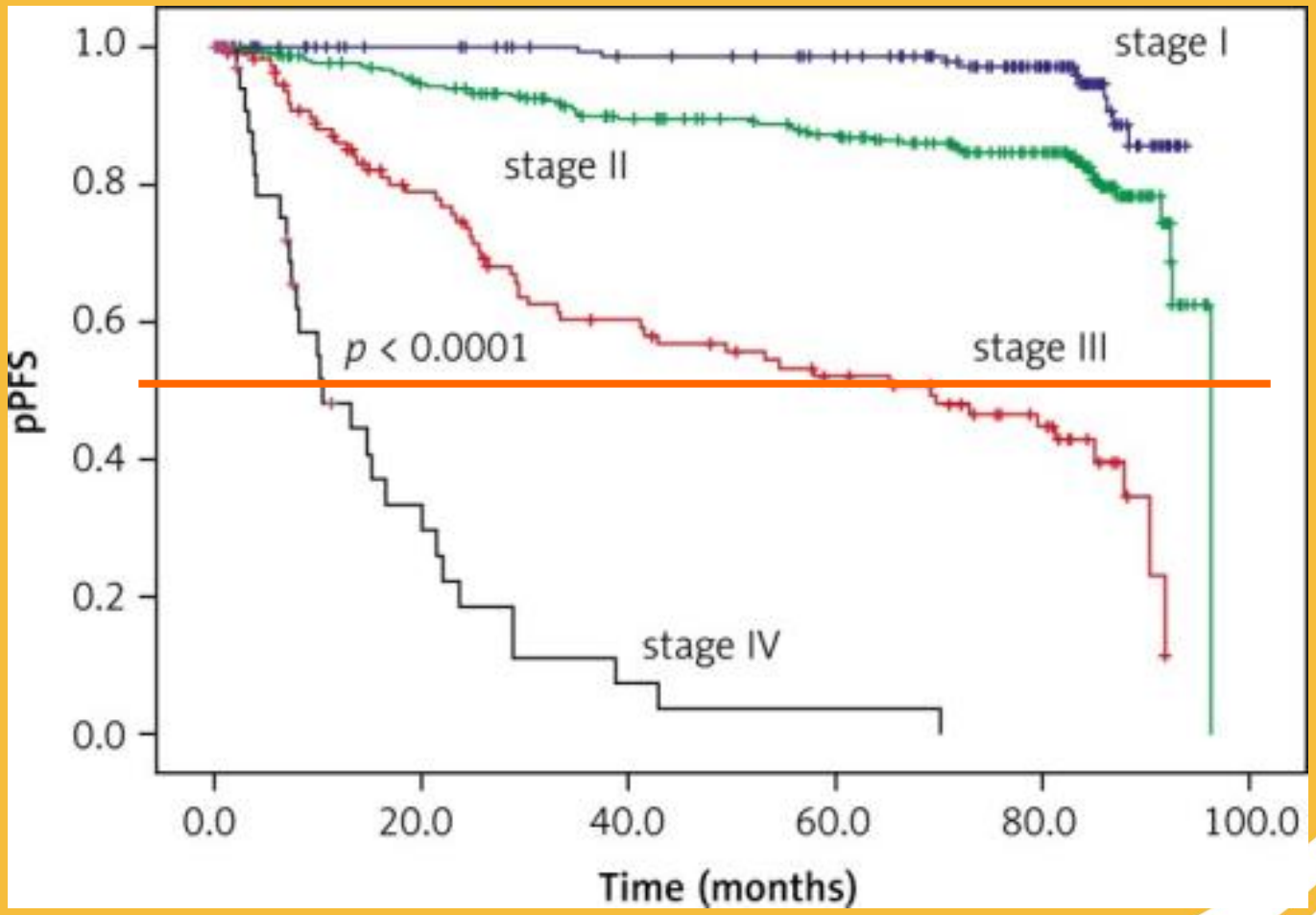
Kaplan–Meier method

	ni	Ci	di	qi= di/ni	Pi=1-qi	Si=pi(pi-1)
Event time (mo)	No at risk	Censor	No of events	Mortality	Survival	Cum survival
3	10	0	1	1/10=0.1	0.90	0.9
4	9	1	0	0/9=0	1.0	0.9*1=0.9
5.7	8	1	0	0/8=0	1.0	0.9*1*1=0.9
6.5	7	0	2	2/7= 0.28	0.72	0.9*1*1*0.72=0.648
.						
10						

Kaplan-Meier survival estimate



Disease-free survival probability of breast cancer patients



Contemp Oncol (Pozn). 2015;19(4):284-9. doi: 10.5114/wo.2015.54387. Epub 2015 Sep 28

Survival Probability

- The proportion of population of such people who survive a given length of time in the same circumstances.
- An estimate of survivorship function S(t) is the estimated proportion of individual who **survive longer than time**

$$S(t_j) = S(t_{j-1})\left(1 - \frac{d_j}{n_j}\right)$$

$S(t_j)$ คือ survival function หรือ probability of survival at time t_j
$S(t_{j-1})$ คือ probability of survival at time t_{j-1}
n_j คือ number of patients alive just before t_j
d_j คือ number of events at t_j

Hazard function

- Hazard function h(t) is the probability that an individual **die (fail) at time t**, conditional on s/he's having survived before time t.
- In another word, the hazard function is the death rate for an individual surviving at time t.

Hazard ratio

- **Hazard ratio** (HR) is a measure of **an effect** of **an intervention** on **an outcome** of interest over time.

Because Hazard Ratio is a ratio, then when:

HR = 1: at any particular time, event rates are the **same** in both groups,

HR = 0.5: at any particular time, **half** as many patients in the treatment group are experiencing an event compared to the control group.

HR = 2: at any particular time, **twice** as many patients in the treatment group are experiencing an event compared to the control group.

Interpreting hazard ratio

- In the results, the authors reported that the hazard ratio for death with the new treatment = **0.38 (95% CI, 0.28-0.53; P<0.0001)**.
- What does that mean?

Interpreting hazard ratio

- In the results, the authors reported that the hazard ratio for death with the new treatment = **0.38 (95% CI, 0.28-0.53; P<0.0001).**

- Patients in the new treatment group at any time point during the study period were 62% less likely to die than patients in the control group, and we are 95% confident that the true value is lying between 47%-72%.

Statistical analysis

- Survival analysis with **life table** or **Kaplan-Meier** were used to estimate survival rate, median survival time of recipients.
- **Log-rank test** was used to compare survival curves.
- **Cox regression** was used to determine factors associated with survival time.
- **Likelihood ratio test** was used for model section.

Comparing two survival curves

- Logrank test
- The null hypothesis for comparing survival/failure times is:

$$H_o : S_1(t) = S_2(t) =,..., S_2(t) \quad \text{or}$$

$$H_o : H_1(t) = H_2(t) =,..., H_2(t) \quad \text{or}$$

$$H_o : \text{Median}(t_1) = \text{Median}(t_2) = \text{Median}(t_3)$$

Logrank statistic for survival

- No of patients at risk in Gr1 Gr2
- No of observed events in Gr1 Gr2
- No of expected events in Gr1 Gr2

$$\chi^2 = \frac{(O_1-E_1)^2}{E_1} + \frac{(O_2-E_2)^2}{E_2}$$

Mahidol University
Faculty of Medicine Ramathibodi Hospital
Department of Clinical Epidemiology and Biostatistics

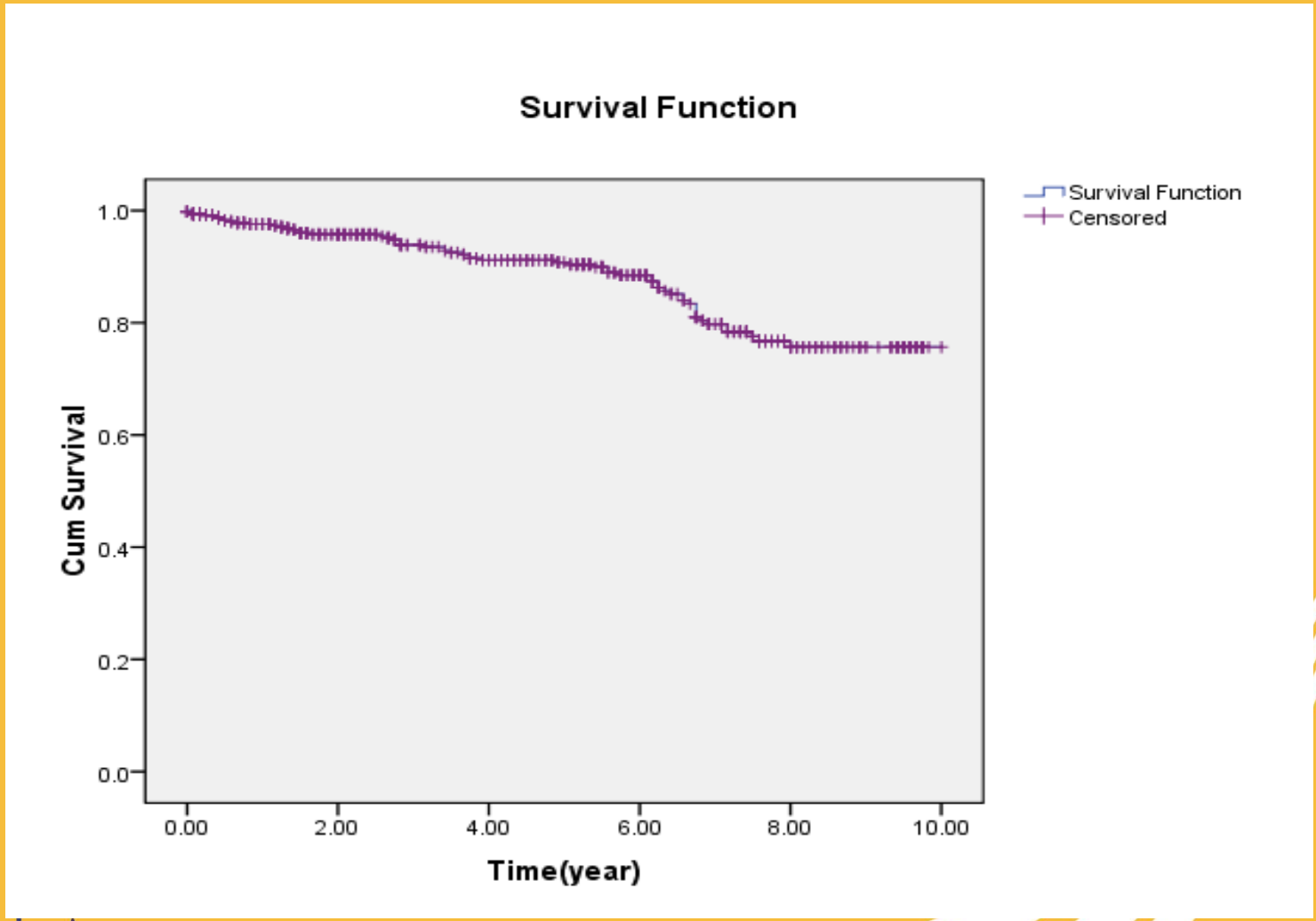
Demonstrating calculation of Log-rank statistics

Time (month)	d_{1j} Number of Deaths	n_{1j} Number at risk	d_{2j}	n_{2j}	d_j	n_j	e1j $= \frac{n_{1j} d_j}{n_j}$	e2j $= \frac{n_{2j} d_j}{n_j}$
.03	1	15	0	15	1	30	1x15/30=.50	1x15/30=.50
.07	1	14	0	15	1	29	1x14/29=.48	1x15/29=.52
.1	1	13	0	15	1	28	1x13/28=.46	1x15/28=.54
.17	1	12	0	15	1	27	.44	.56
.23	1	11	0	15	1	26	.42	.57
.27	1	10	0	15	1	25	.40	.60
.50	1	9	0	15	1	24	.38	.63
3.03	1	8	0	15	1	23	.35	.65
5.93	0	7	1	15	1	22	.32	.68
9.13	1	7	0	14	1	21	.33	.67
9.80	1	6	0	14	1	20	.30	.70
13.23	0	5	1	14	1	19	.26	.74
15.83	0	5	1	13	1	18	.28	.72
Total	10		3				4.93	8.07

$$\chi^2 = \frac{(10-4.93)^2}{4.93} + \frac{(3-8.07)^2}{8.07} = 8.39$$

P=0.001

Death-censored graft survival of renal transplant recipients



Mahidol University
Faculty of Medicine Ramathibodi Hospital
Department of Clinical Epidemiology and Biostatistics

Standard survival analysis vs. competing risk

Standard survival analysis or KM method

- In survival analyses, all subjects who are at risk of experiencing an event are part of the so-called risk set.
- The risk set usually consists at each point in time of individuals who have been followed-up till that time and have not yet experienced the event of interest just before that time point.
- The survival time of subjects who do not experience the outcome of interest during the observation period is **censored** at the end of follow-up.

Censoring

- In those cases, we do not know whether and when such a patient will experience the event, we only know that he or she has not done so by the end of the observation period.
- Censoring may occur for various reasons.
  - Loss to F/U
  - Other event
- **An important assumption of standard survival analytical methods such as the Kaplan–Meier method is that censoring is 'independent'**

Issues about censoring assumption

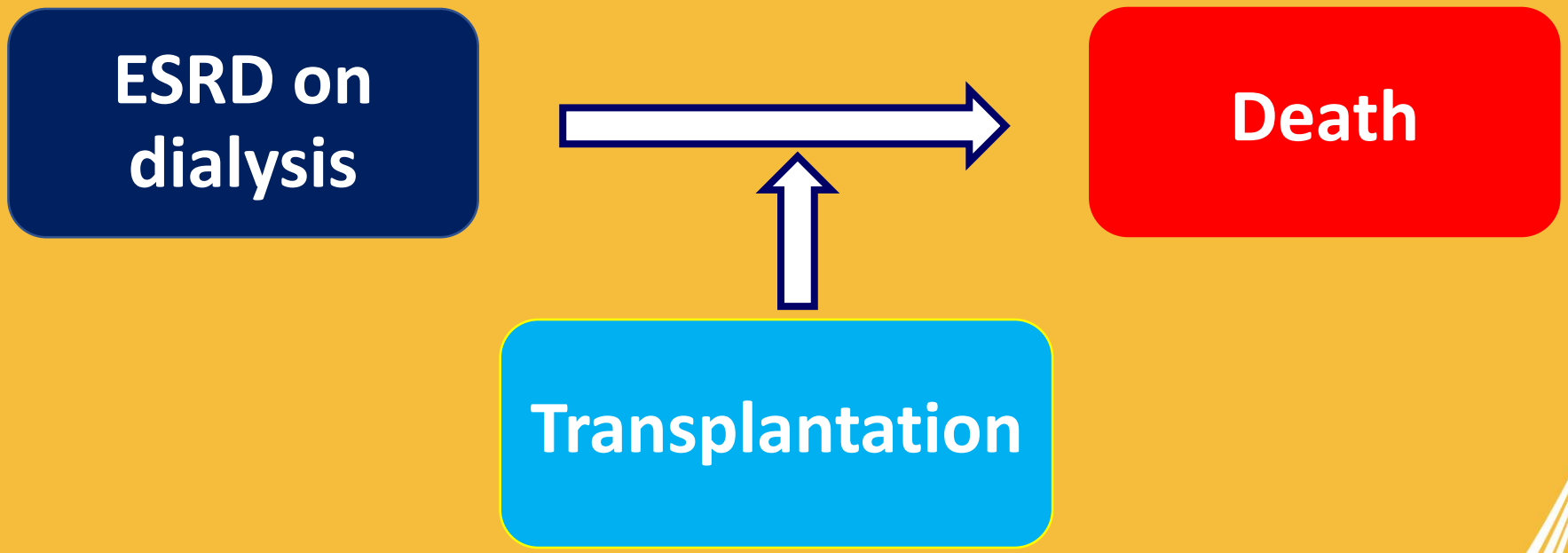
- This independent censoring assumption implies that patients who are censored at a certain time point should be **representative** for those still at risk (and thus in the risk set) at that point in time.
- This is, for example, usually the case when a patient's survival time is censored because he or she was lost to follow-up, for instance, due to migration.
- In this situation, we can assume that this **occurred at random** and patients who are censored are likely to be at a similar risk of experiencing the event of interest as patients who are not.

The problems of competing risk

- A competing risk is an event that either hinders the observation of the event of interest or modifies the chance that this event occurs.
- For example, when performing a study with mortality on dialysis as the outcome of interest, a patient may receive a kidney transplant.

Kaplan Meier product-limit method, are not designed to accommodate the competing nature of multiple causes to the same event.

The problems of competing risk



This transplant is a competing risk because after the transplantation, this patient is not on dialysis anymore and therefore no longer at risk of dying while being on dialysis.

In this case, the competing event, i.e. receiving a kidney transplant, hinders the occurrence of the event of interest.

Mahidol University
Faculty of Medicine Ramathibodi Hospital
Department of Clinical Epidemiology and Biostatistics

Competing risk in prognostic research

1. To estimate the unadjusted probability of a certain outcome
2. To estimated the adjusted probability
3. To determine the association

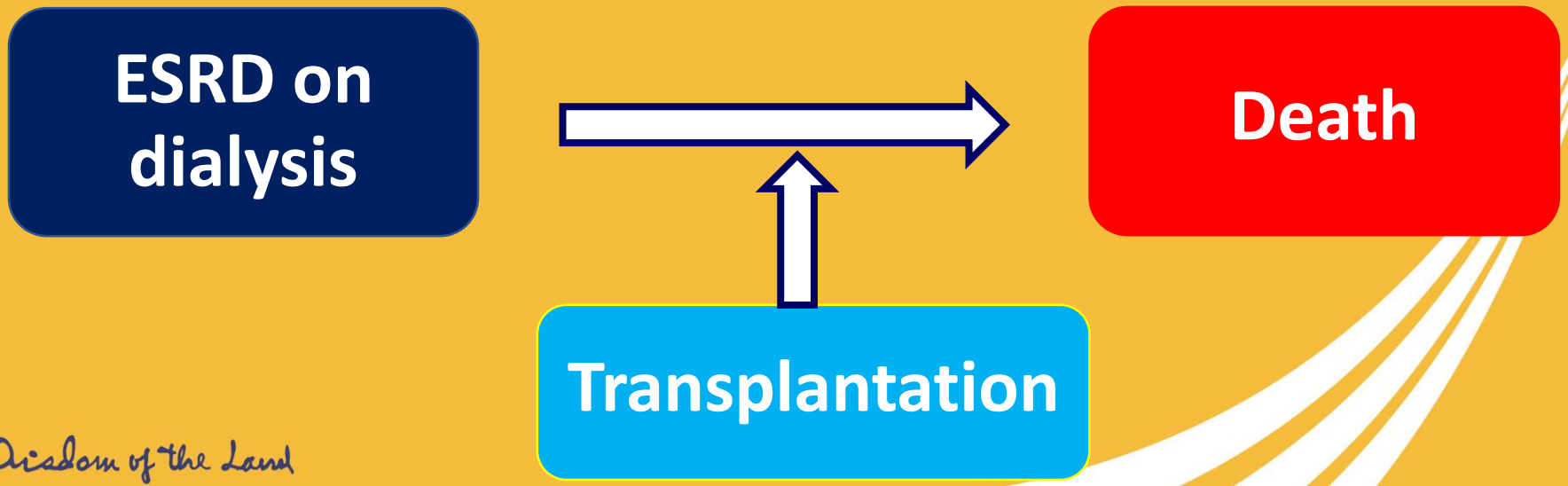
Unadjusted probability

- The **cumulative incidence competing risk (CICR)** method, is based on the so-called **cumulative incidence function**.
- The CICR accounts for all types of events; in the case of competing events, the cumulative incidence function is estimated both
  - The event of interest
  - The competing events,

  and their estimates depend on each other.
- The probability of dying before time t, is lowered by the occurrence of the competing event and patients experiencing the **competing event are considered to be no longer at risk** for the event of interest.

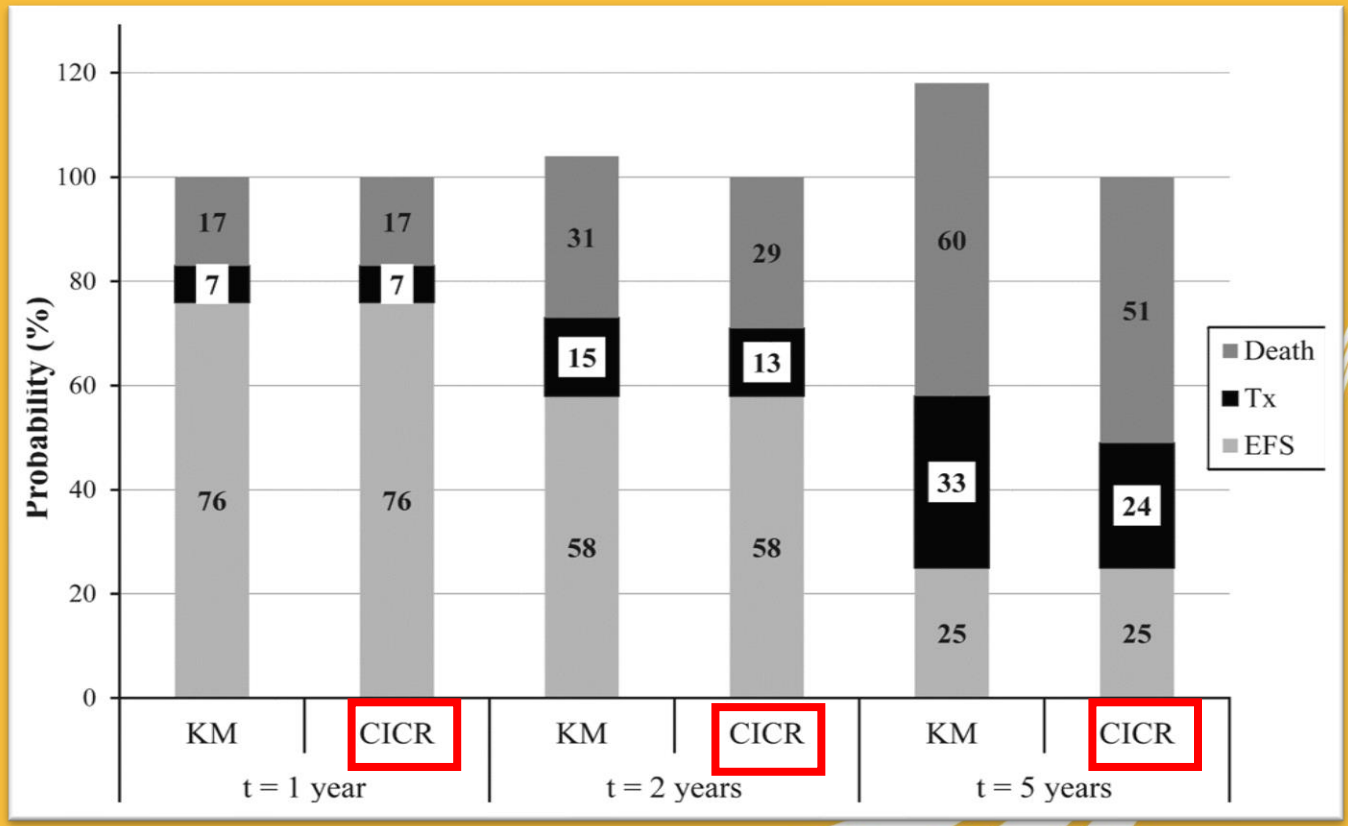
Example

- Using ERA-EDTA Registry data, a study of patient survival from Day 91 after the start of dialysis with death on dialysis as the event of interest.
- Kidney transplantation is the competing event because a patient who receives a transplant is no longer at risk of death on dialysis.
- The probability of being alive and not having received a kidney transplant at a given time t is given by the event-free survival (EFS) probability.



- Conventional methods for survival analysis ignoring the competing event(s), such as the Kaplan–Meier(KM) method and standard Cox proportional hazards regression, may be inappropriate in the presence of competing risks.
- KM→ **overestimate** survival probability and **increasing** with follow up time.
- In other word, KM→ **underestimate** death probability.

Cumulative incidence competing risk (CICR)

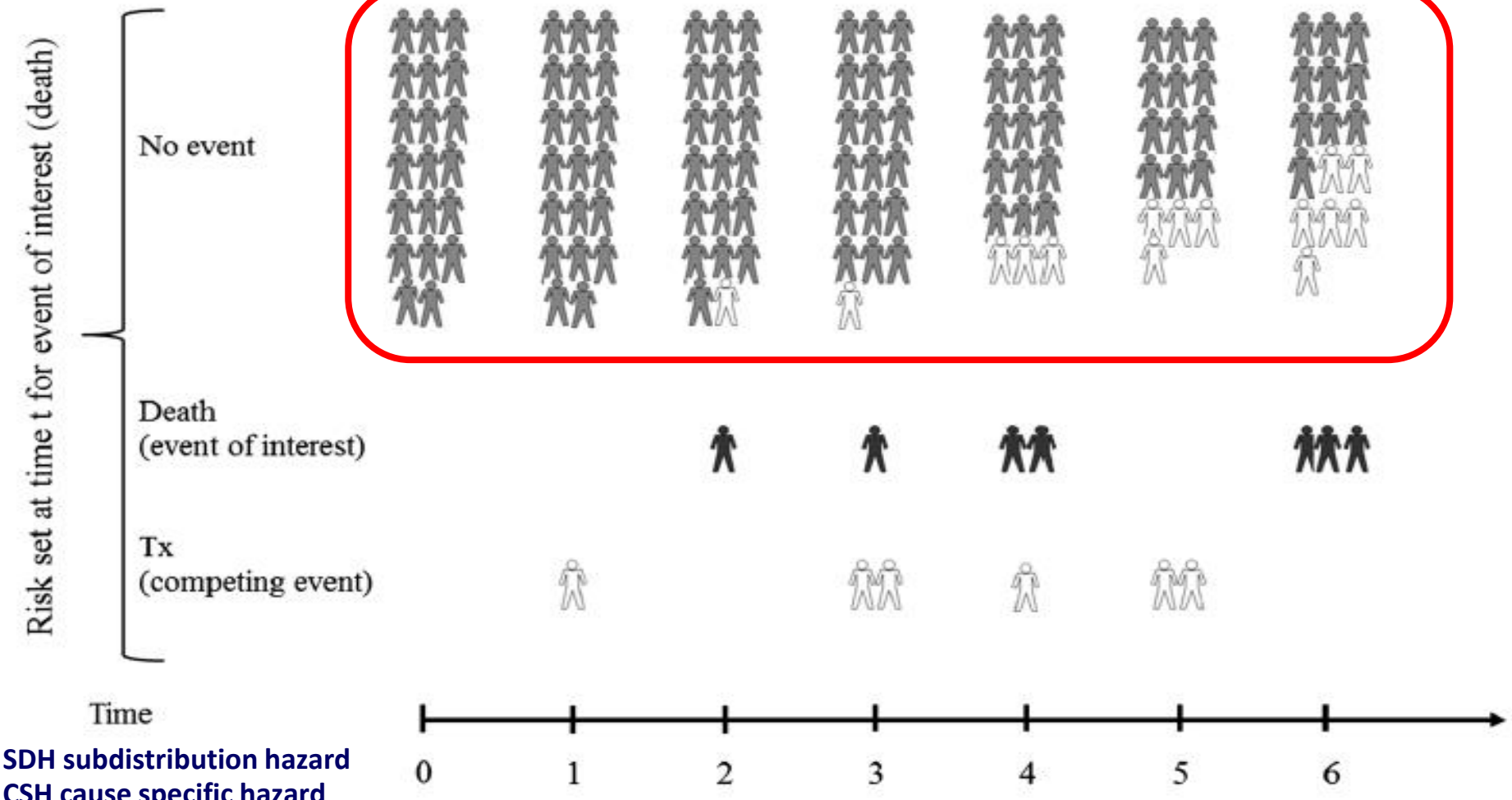


Adjusted probability

- The **subdistribution hazards** approach proposed by Fine and Gray [20] is the most appropriate method to use for competing risks regression.
- An important feature of this method is that **subjects who experience a competing event remain in the risk set** (instead of being censored), although they are in fact no longer at risk of the event of interest.

Subdistribution hazard approach

Risk set remove only death



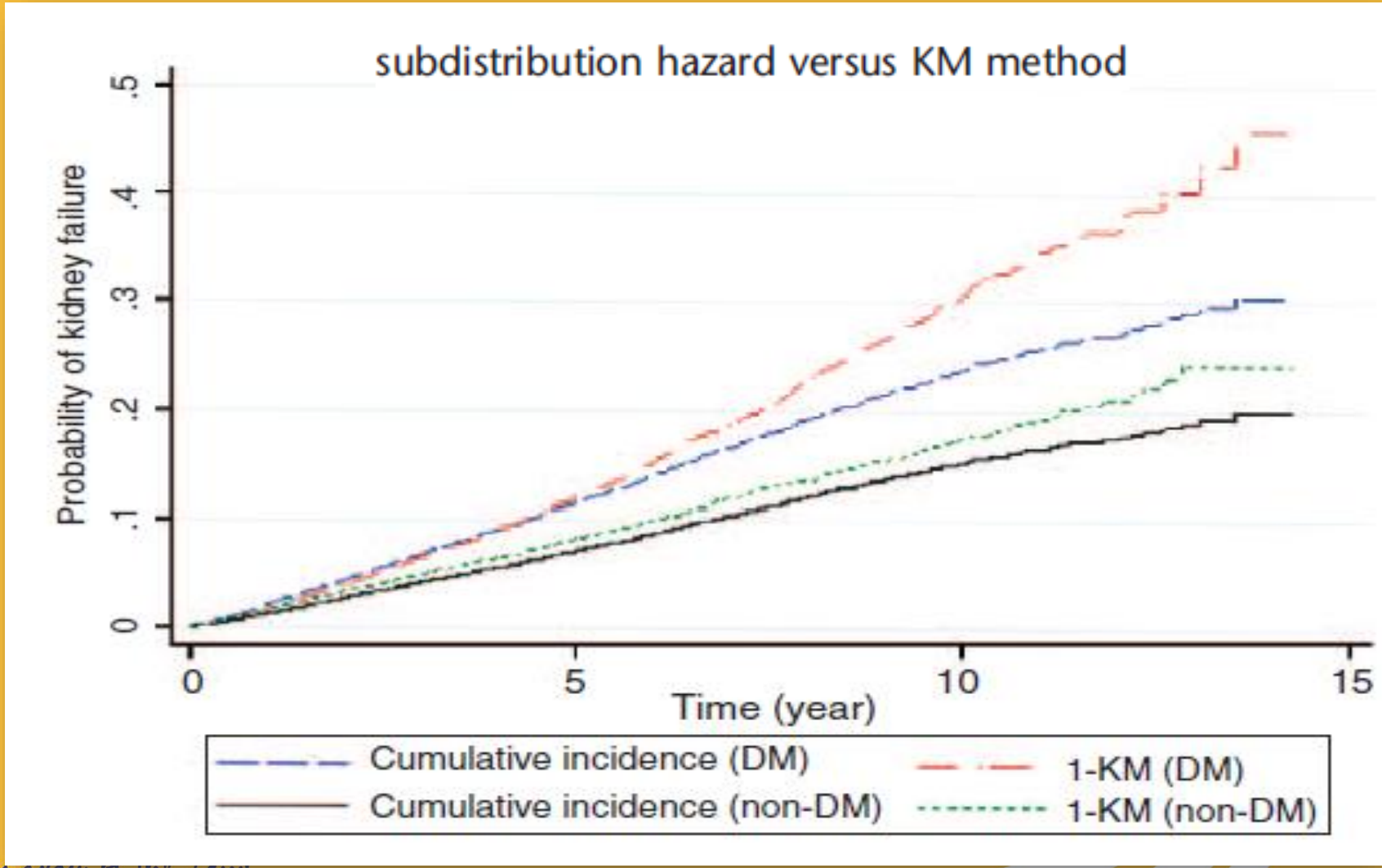
SDH subdistribution hazard
CSH cause specific hazard

Hazard (t)	t=0	t=1	t=2	t=3	t=4	t=5	t=6
SDH	0/20=0	0/20=0	1/20=0.05	1/19=0.05	2/18=0.11	0/16=0	3/16=0.19

Subdistribution hazards approach

- As a consequence, the subdistribution HR (SHR) resulting from this method cannot be interpreted as an HR.
- However, when used for prediction, the SHR is only used as part of the calculation of an individual patient's risk.

Estimation of probability of ESRD



Determine association: HR in competing risk

- The proportional cause-specific hazards model may be more appropriate than the subdistribution hazards method.
- This is because the regression parameters estimated by this method directly quantify the HRs among those individuals who are actually at risk of developing the event of interest.
- So, **separate Cox regression models** are used to study the event of interest, for example, death on dialysis and the competing event(s), transplantation.

Cause-specific hazards model

- In each of these models, the **competing events are treated as censored** observations.
- Note that one does not need the independence of competing events to obtain valid estimates from such a cause-specific approach.

Cause-specific approach

Risk set remove both death and Tx

Hazard (t)	t=0	t=1	t=2	t=3	t=4	t=5	t=6
Death	0/20=0	0/20=0	1/19=0.05	1/18=0.06	2/15=0.13	0/12=0	3/10=0.33
Tx	0/20=0	1/20=0.05	0/19=0	2/18=0.11	1/15=0.07	2/12=0.17	0/10=0

Cause-specific hazards model

- Because the competing events are treated as censored observations, during follow-up, the number of patients at risk is reduced.
- Therefore, HRs calculated using this approach are interpreted as **'among those patients who did not (yet) experience the event of interest or a competing event'**.

Interpretation csHR

- The HR of 2.57 means that at any time after dialysis initiation among patients on dialysis who were alive and did not receive a transplant at that time, dialysis patients older than 65 years had a hazard of dying 2.57 times higher than those younger than 65 years.

Mahidol University
Faculty of Medicine Ramathibodi Hospital
Department of Clinical Epidemiology and Biostatistics

EBM

Scenario

- You're an doctor at Ramathibodi hospital.
- A 70-year-old woman who diagnosed as chronic kidney disease from diabetes mellitus was came to your OPD at this morning. Her serum BUN and creatinine were 70 and 4.0 (eGFR = 12 ml/min/1.73m^2)
- She denied any uremic symptoms.

  - **You wonder about the appropriate timing of dialysis initiation for this patient whether early or late dialysis would be the better.**

Mahidol University
Faculty of Medicine Ramathibodi Hospital
Department of Clinical Epidemiology and Biostatistics

Step 1: Ask answerable question

Converting a clinical problem into a clinical question

- P 70 years old woman with end-stage renal disease
- I Early dialysis
- C Late dialysis
- O Survival rate

Step 2: Find an Article

1. Formulate your PICO question
2. Try secondary sources
3. Choose primary database(s)
4. Combine text words
5. Filter for the right type of study

Mahidol University
Faculty of Medicine Ramathibodi Hospital
Department of Clinical Epidemiology and Biostatistics

Your PICO → search term

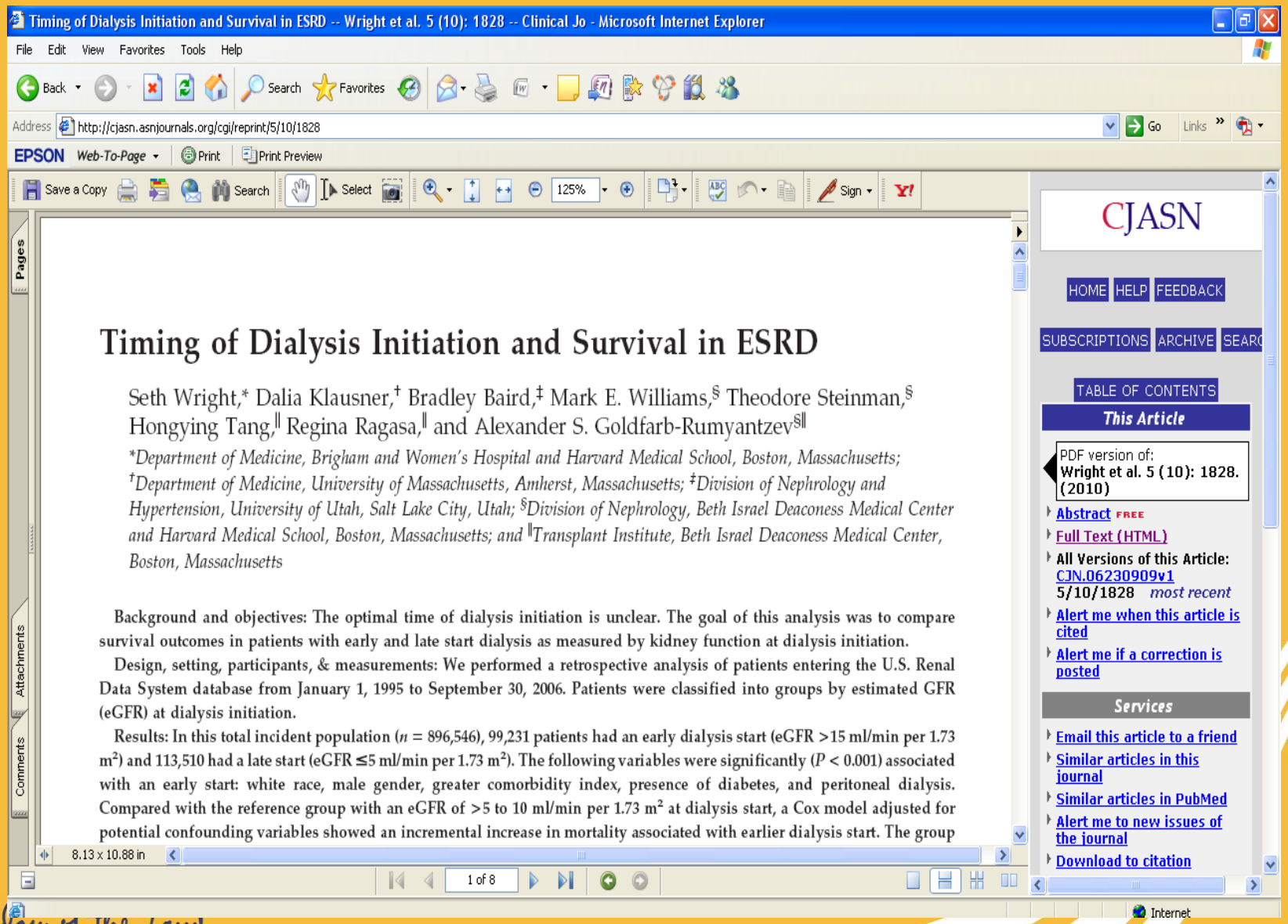
ส่วนประกอบ	ตัวอย่าง	Search term
P = Population	Among end-stage renal disease,	end-stage renal disease, ESRD
I = Intervention	Would treating with early dialysis	Early dialysis
C = Comparison	Compared with late dialysis	Late dialysis
O = Outcome	Have different survival rate	Survival rate

How to choose the right article(s)?

How to choose the right article(s)?

- Relevant
  - P
  - I
  - C
  - O
- High impact factor journal
- Appropriate study design
- Up date
- Well-known authors

Find Articles



Mahidol University
Faculty of Medicine Ramathibodi Hospital
Department of Clinical Epidemiology and Biostatistics

Step 3: Critical Appraisal the evidence

Users' Guide to the Medical Literature

Guyatt GH, Rennie D. Users' guides to the medical literature. 2015


Dr. Gordon Guyatt

Mahidol University
Faculty of Medicine Ramathibodi Hospital
Department of Clinical Epidemiology and Biostatistics

Users' Guides to an article about prognosis

A. How serious is the risk of bias?

B. What are the results?

C. How can I apply the results to patient care?

Mahidol University
Faculty of Medicine Ramathibodi Hospital
Department of Clinical Epidemiology and Biostatistics

A. How serious is the risk of bias?

1. Was the sample of patients **representative**?
2. Were the patient classified into **prognostically similar** groups?
3. Was follow-up sufficiently **complete**?
4. Were **outcome** criteria objective and unbiased?

A. How serious is the risk of bias?

1. Was the sample of patients **representative**?

A. How serious is the risk of bias?

1. Was the sample of patients **representative**?

- Representativeness
  - How close to “ideal” does the study come in terms of how the disease was defined
  - How the participants were assembled (“full spectrum of illness”).

Referral bias?

Recognize an unrepresentative sample

- Determine whether patients pass through some sort of **filter** before entering the study.
  - **Referral bias**
    - Population-based vs. Hospital-based studies
    - Tertiary center often care for patients with rare and complicated.
- **Patients should also be representative of the underlying population. Patients from tertiary referral centers may have more advanced disease and poorer prognoses than patients form primary care.**
- The Methods section should also provide information about patient recruitment, whether patients were recruited from primary care or tertiary referral centers.

A. How serious is the risk of bias?

1. Was the sample of patients **representative**?

Study Population

Institutional review board approval was requested, and this study was determined to have an exempt status as a retrospective analysis of existing de-identified data. The data collected by the USRDS between January 1, 1995 and September 30, 2006 in the PATIENTS, MEDEVID, and RXHIST60 files were used. Adult patients (≥18 years old) on hemodialysis and peritoneal dialysis were included in the study. Patients were excluded from the primary analysis if they had subsequent renal transplantation, recovered renal function, or had values outside of the plausible ranges for height (120 to 200 cm), weight (23 to 180 kg), or body mass index (10 to 60 kg/m^2). Independent variable values that

Selection bias

- Early dialysis start might have some reasons
  - Volume overload
  - Acute illness

A. How serious is the risk of bias?

2. Were the patient classified into **prognostically similar** groups?

What is the best?	Where do I find the information?
It is preferable if study patients are enrolled at a **uniformly early** time in the disease usually when disease first becomes manifest. Such groups of patients are called an **'inception cohort'**.	• The Methods section should describe **the stage** at which patients entered the study (e.g., at the time of first myocardial infarction; Stage 3 breast cancer).

Susceptibility bias

- Groups being compared are not equally susceptible to the outcome of interest, other than the factor under study.

A. How serious is the risk of bias?

2. Were the patient classified into **prognostically similar** groups?

late

Early

Table 1. Baseline characteristics of the study population (n = 896,546)

	Entire Study Population (n = 896,546)[a]	eGFR ≤ 5 ml/min per 1.73 m² (n = 113,510)	eGFR >5 to 10 ml/min per 1.73 m² (n = 463,277)	eGFR >10 to 15 ml/min per 1.73 m² (n = 220,528)	eGFR > 15 ml/min per 1.73 m² (n = 99,231)
Age (years)	64.7 (14.5)	59.3 (15.8)	64.2 (14.3)	66.9 (13.8)	68.4 (13.6)
Sex: male (%)	53.1	44.1	51.7	57.4	60.8
Height (cm)	167.5 (11.0)	166.6 (11.0)	167.5 (11)	167.9 (11.1)	168 (11.2)
Weight (kg)	75.2 (21.4)	73.6 (21.4)	75.3 (21.4)	75.7 (21.4)	75.5 (21.5)
Body mass index (kg/m²)	26.8 (7.3)	26.5 (7.2)	26.8 (7.3)	26.9 (7.3)	26.7 (7.3)
Race (%)					
White	64.2	55.4	63.6	67.4	70
African American	29.8	35.4	30.1	28	26.2
Native American	1.2	1.6	1.3	1.0	0.8
Asian	3.4	5.4	3.6	2.7	2.2
Other	1.3	2.3	1.4	0.9	0.8
Cause of ESRD (%)					
Diabetes	46.7	30	46.1	53.5	53.4
Hypertension	28.4	32.1	28.6	27	26.9
Glomerulonephritis	7.3	12.5	7.8	5.1	3.8
Cystic kidney disease	1.5	2.4	1.8	1.0	0.5
Other urologic	2.5	4.0	2.4	2.1	2.5
Other cause	9.7	12.9	9.8	8.1	9.2
Unknown cause	3.8	6.1	3.6	3.2	3.8
History of diabetes (%)	56.2	37.1	55.1	64.1	66.2
Charlson comorbidity index	7.0 (2.3)	5.9 (2.4)	6.9 (2.2)	7.5 (2.1)	7.8 (2.1)

If subgroups with different prognosis are identified, did adjustment for important prognostic factors take place?

What is the best?	Where do I find the information?
▪ A prognostic factor is a patient characteristic (e.g., age, stage of disease) that predicts the patient's eventual outcome. ▪ The study should **adjust** for known prognostic factors in the analysis so that results are not distorted.	▪ The ***Results*** section should identify any prognostic factors and whether or not these have been adjusted for in the **analysis.** ▪ Also look at the tables and figures for evidence of this (e.g., there may be separate survival curves for patients at different stages of disease or for different age groups).

Methods for controlling Susceptibility bias

Method	Phase of study	
	Design	Analysis
Randomization	+	
Restriction	+	
Matching	+	
Stratification		+
Adjustment		+

Propensity score matching (PSM)

- A statistical matching technique that attempts to estimate the effect of a treatment, policy, or other intervention by accounting for the covariates that predict receiving the treatment.
- PSM attempts to reduce the bias due to confounding variables that could be found in an estimate of the treatment effect obtained from simply comparing outcomes among units that received the treatment versus those that did not.

Method: Statistical plan

Multivariate Models and Covariates

The Cox models were adjusted for covariates believed to be potential confounders that could be related to both the outcome and the primary variable of interest. All multivariate models were adjusted for the following variables at ESRD onset: age, height, weight, race, gender, diabetic status, comorbidity index (described below), duration of pre-dialysis nephrology care, type of dialysis, type of vascular access, and cause of ESRD. The comorbidity index for each subject was calculated based on the Charlson index (9), with a method using only the terms available in the dataset (10): age, history of myocardial infarction, congestive heart failure, ischemic heart disease, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, cancer, and diabetes. Both the Charlson index and history of diabetes were included separately in the Cox models because diabetic status is a significant predictor of outcomes, and its effects cannot be completely explained by the Charlson index. The lack of colinearity between diabetic status and the Charlson index was confirmed before analysis.

Confounders

- Residual confounders
  - Dialysis dose: KT/V
  - Anemia
  - Volume status
  - Nutritional status: albumin
  - Calcium, Phosphate, parathyroid hormone
  - Reason for dialysis initiation
  - etc.

A. How serious is the risk of bias?

3.Was follow-up sufficiently complete?

- Those who are followed up may have systematically higher or lower risk than those not followed up.

What is the best?	Where do I find the information?
▪ **All patients** should be followed from the beginning of the study until the outcome of interest or death occurs. ▪ **Reasons for non follow-up** should be provided along with comparison of the demographic and clinical characteristics of the patients who were unavailable and those in whom follow-up was complete.	• The ***Results*** section should also provide the number of and the reasons for patients being unavailable for follow-up. • A comparison of the two groups (those available and those unavailable) may be presented in table form or the authors may simply state in the text whether or not there were differences.

A.How serious is the risk of bias?

3.Was follow-up sufficiently complete?

- Those who are followed up may have systematically higher or lower risk than those not followed up.

What is the best?	Where do I find the information?
▪ All patients should be followed from the beginning of the study until the outcome of interest or death occur ▪ **Reasons for** be provided comparison and clinical characteristics of the patients who were unavailable and those in whom follow-up was complete.	• The ***Results*** section should also provide the number of and the reasons for patients being w-up. e two groups l those e presented in table form or the authors may simply state in the text whether or not there were differences.

How many patients lost to follow-up is too many?

Mahidol University
Faculty of Medicine Ramathibodi Hospital
Department of Clinical Epidemiology and Biostatistics

When does loss to follow-up seriously threaten validity?

	Study A		Study B	
	Treatment	Control	Treatment	Control
No. of patients	1000	1000	1000	1000
No. of lost to F/U	30 (3%)	30 (3%)	30 (3%)	30 (3%)
No. of death	200 (20%)	400 (40%)	30 (3%)	60 (6%)
RRR not counting patient lost to F/U	(0.4-0.2)/0.4=0.2/0.4 = 0.50		0.03/0.06 = 0.50	
RRR for worst-case scenario	(0.4-0.23)/0.4=0.17/0.4 = **0.43**		0.00/0.06 = **0**	

A. How serious is the risk of bias?

3. Was follow-up sufficiently complete?

Timing of Dialysis Initiation and Survival in ESRD

Seth Wright,* Dalia Klausner,† Bradley Baird,‡ Mark E. Williams,§ Theodore Steinman,§ Hongying Tang,‖ Regina Ragasa,‖ and Alexander S. Goldfarb-Rumyantzev§‖

*Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; †Department of Medicine, University of Massachusetts, Amherst, Massachusetts; ‡Division of Nephrology and Hypertension, University of Utah, Salt Lake City, Utah; §Division of Nephrology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts; and ‖Transplant Institute, Beth Israel Deaconess Medical Center, Boston, Massachusetts

- Follow-up complete from national database

A. How serious is the risk of bias?

4. Were outcome criteria objective and unbiased?

- A clear definition of all outcomes should be provided.
- It is ideal if less objective outcomes are assessed blindly, that is, the individual determining the outcome does not know whether the patient has a potential prognostic factor.
  - Objective: death
  - Require some judgment: myocardial infarction
  - Require considerable judgment and effort to measure: disability, quality of life

Measurement bias

- When members of the cohort are not all **assessed similarly** for outcome.

- Misclassification bias: non-differential
  - Acute MI ↔ No acute MI

Primary outcome measurement

The outcome variable was patient survival from the time of dialysis initiation (variable FIRST_SE) to patient's death (variable DIED) or censor at September 30, 2006, which was the end of the available dataset. The causes of death recorded in the USRDS database were grouped into cardiovascular, infection, malignancy, and other causes.

Valid?

0% 100%

If so, we proceed……!

Mahidol University
Faculty of Medicine Ramathibodi Hospital
Department of Clinical Epidemiology and Biostatistics

A. How serious is the risk of bias?

1. Was the sample of patients **representative**?

±

2. Were the patient classified into **prognostically similar** groups?

3. Was follow-up sufficiently **complete**?

4. Were **outcome** criteria objective and unbiased?

B. What are the results?

1. How likely are the outcomes over time?

2. How precise are the estimates of likelihood?
   - 95%CI

Results

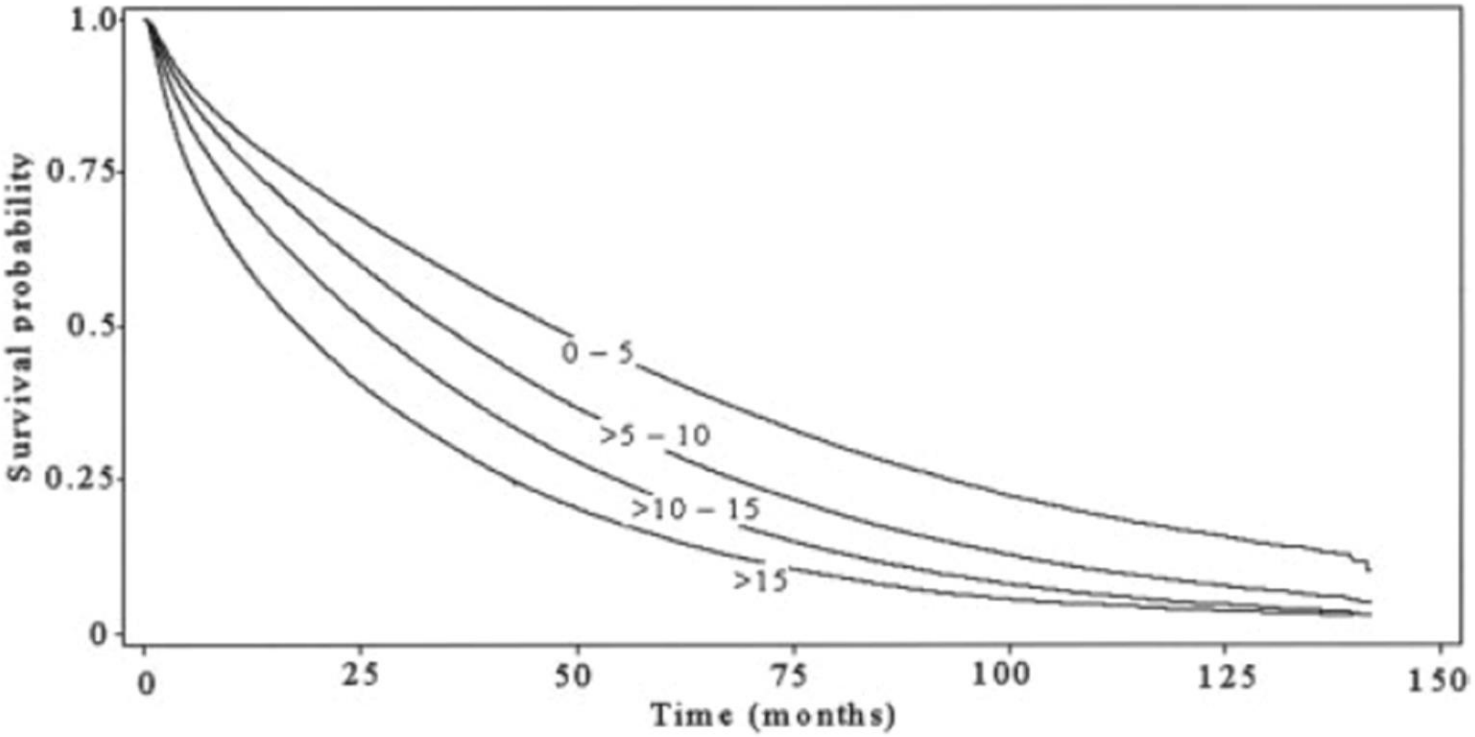


Figure 1. Kaplan-Meier survival curves (survival *versus* time after dialysis initiation) for categories of patients divided by the residual renal function (eGFR, ml/min per 1.73 m^2) at the initiation of dialysis.

Results

Median time

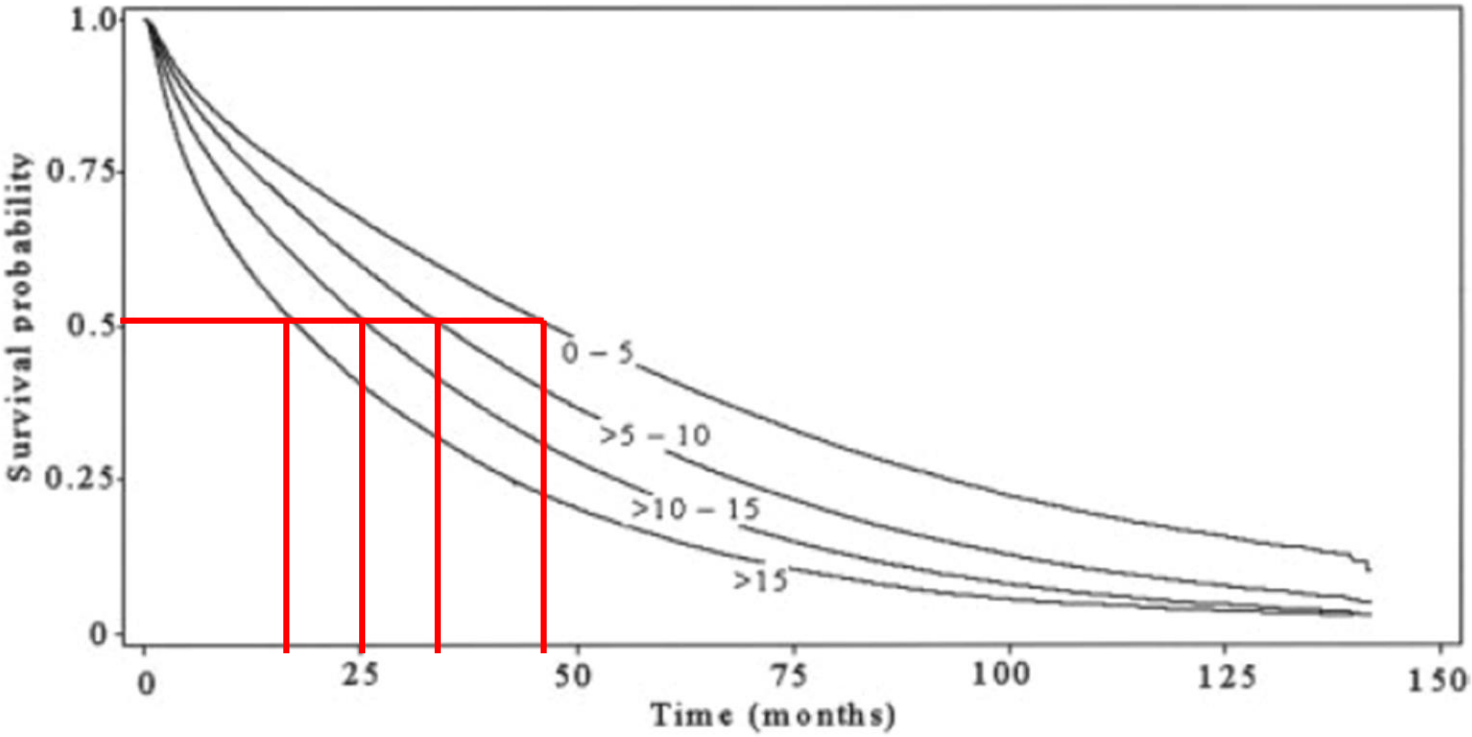


Figure 1. Kaplan-Meier survival curves (survival *versus* time after dialysis initiation) for categories of patients divided by the residual renal function (eGFR, ml/min per 1.73 m^2) at the initiation of dialysis.

How precise are the estimates of likelihood?

Table 3. Effect of timing of dialysis start on patient survival using Cox models in the entire study population and patient subgroups[a]

	HR (95% CI)	*P*
Entire study population (n = 895,293)[b]		
eGFR >15 ml/min per 1.73 m^2	1.44 (1.43 to 1.45)	<0.001
eGFR >10 to 15 ml/min per 1.73 m^2	1.15 (1.15 to 1.16)	<0.001
eGFR >5 to 10 ml/min per 1.73 m^2	Reference	
eGFR ≤5 ml/min per 1.73 m^2	0.88 (0.87 to 0.88)	<0.001
Age categories[b]		
Patients younger than 75 yr (n = 651,304)		
eGFR >15 ml/min per 1.73 m^2	1.48 (1.46 to 1.49)	<0.001
eGFR >10 to 15 ml/min per 1.73 m^2	1.17 (1.16 to 1.17)	<0.001
eGFR >5 to 10 ml/min per 1.73 m^2	Reference	
eGFR ≤5 ml/min per 1.73 m^2	0.86 (0.85 to 0.86)	<0.001
Patients 75 or older (n = 243,989)		
eGFR >15 ml/min per 1.73 m^2	1.35 (1.33 to 1.37)	<0.001
eGFR >10 to 15 ml/min per 1.73 m^2	1.11 (1.10 to 1.26)	<0.001
eGFR >5 to 10 ml/min per 1.73 m^2	Reference	
eGFR ≤5 ml/min per 1.73 m^2	0.96 (0.94 to 0.97)	<0.001

[a]Only primary variables of interest are presented in the table. All models were adjusted for the following covariates: age at ESRD onset, height and weight at the time of ESRD onset, race, sex, diabetic status, Charlson comorbidity index, duration of pre-dialysis nephrology care, type of dialysis, type of vascular access, and cause of ESRD.

[b]The number of subjects may be less than the entire study population because of missing variables.

C. How can I apply the results to patient care?

1. **Were the study patients and their management similar to those in my practice?**
   - Describe the study patients explicitly and in detail.
   - Treatment strategies may vary over time.

2. **Was follow-up sufficiently long?**
   - Investigators must follow up patients for a period long enough to detect the outcomes of interest.

Was follow-up sufficiently long?

What is the best?	Where do I find the information?
▪ **Length of follow-up** should be long enough to detect the outcome of interest. ▪ This will vary depending on the outcome (e.g., for pregnancy outcomes, nine months; for cancer, many years).	▪ The ***Results*** section should state the median or mean length of follow-up.

C. How can I apply the results to patient care?

3. Can I use the study results in the management of patients in my practice?

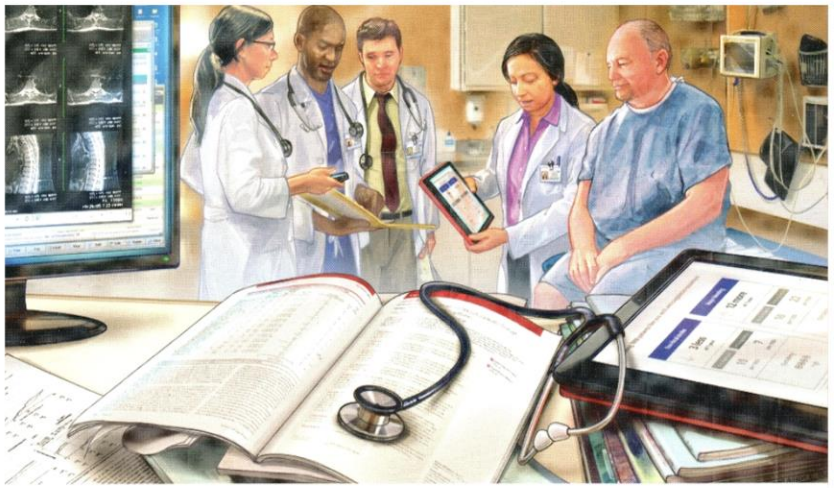
- Prognostic results may help you with
  - Selection of treatment
  - Counseling
    - Non-disease
    - End-of-life care

Prognosis

- An inception cohort of persons, all initially free of the outcome of interest
- Representative of sample
- Homogenous to prognostic risk
- Objective outcome measurement
- Follow-up complete
- Survival analysis

Mahidol University
Faculty of Medicine Ramathibodi Hospital
Department of Clinical Epidemiology and Biostatistics

Suggested reading



3rd EDITION

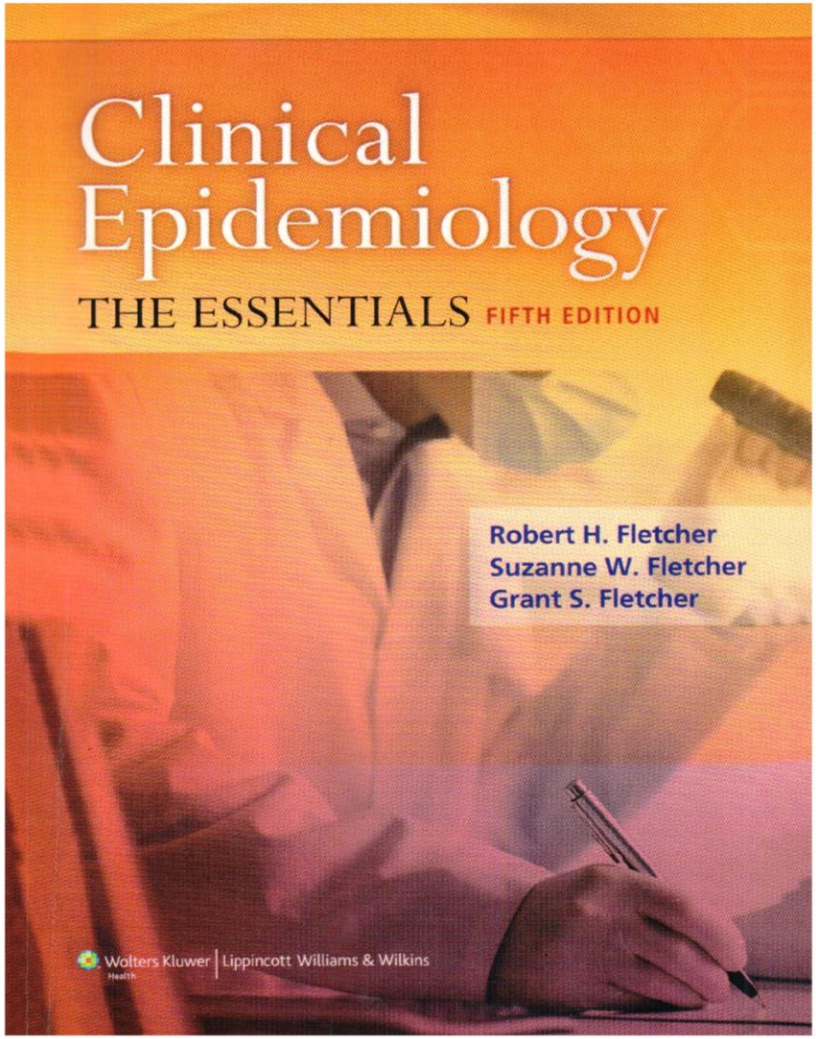
Users' Guides to the Medical Literature

A MANUAL FOR EVIDENCE-BASED CLINICAL PRACTICE

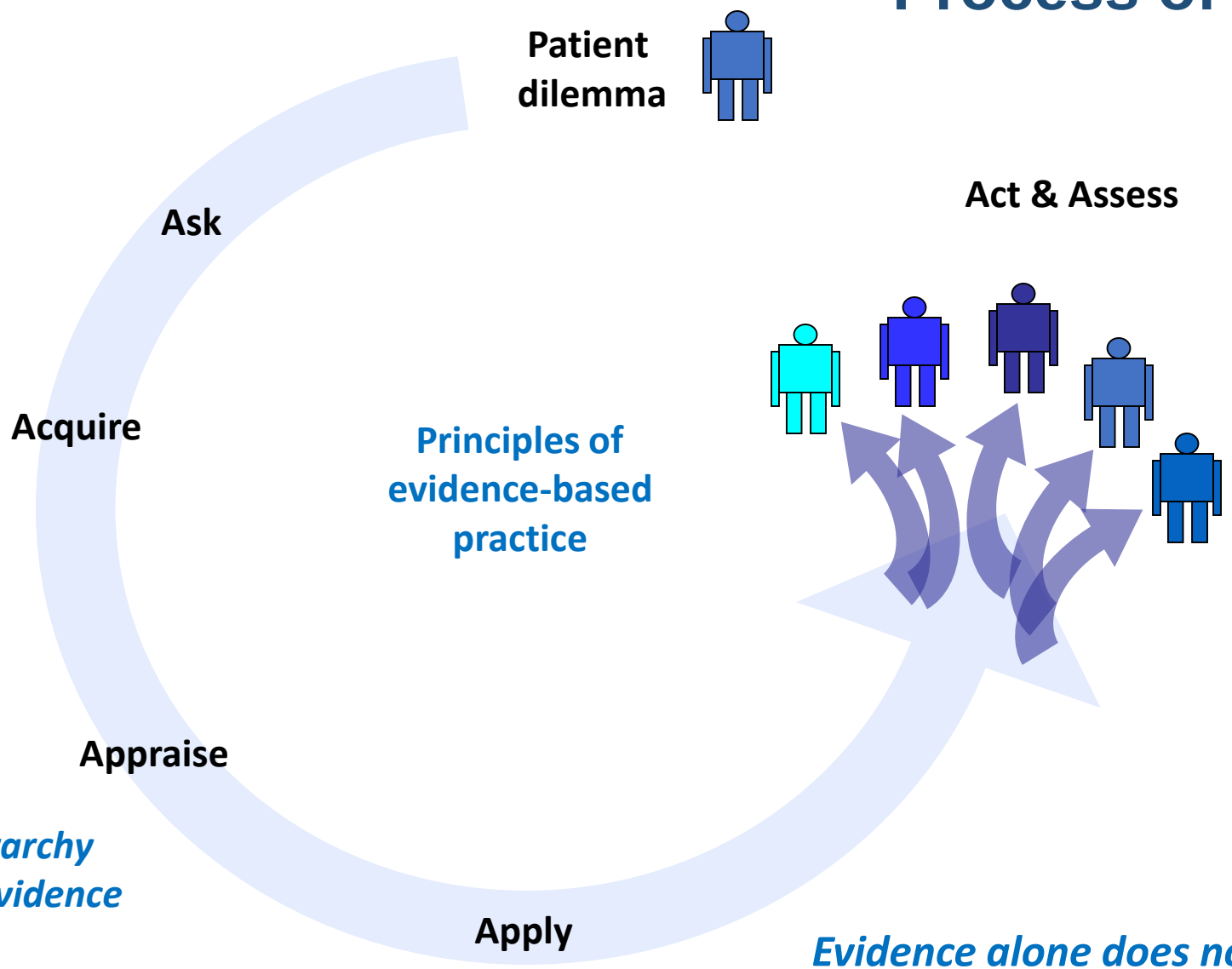
Gordon Guyatt, MD
Drummond Rennie, MD
Maureen O. Meade, MD
Deborah J. Cook, MD

Mc Graw Hill Education

JAMAevidence



Process of EBP



Evidence alone does not decide – combine with other knowledge and values

Mahidol University
Faculty of Medicine Ramathibodi Hospital
Department of Clinical Epidemiology and Biostatistics

Thank you

Department of Epidemiology and Biostatistics

Faculty of Medicine
Ramathibodi Hospital, Mahidol University