Early utilization of hypertonic peritoneal dialysate and subsequent risks of non-traumatic amputation among peritoneal dialysis patients: A nationwide retrospective longitudinal study

Shih-Yi Lin[1,2], Che-Chen Lin, MS[3,4], Chung-Chih Lin[2], Chi-Jung Chung [5,6], Horng-Che Yeh[2], I-Kuan Wang[1,2], Chiz-Chung Chang [1,2], Chiu-Chin Huang[1,2], Fung-Chang Sung, PhD, MPH[3,4]

林詩怡
中國醫藥大學附設醫院
腎臟科暨腎臟醫學中心

Oral presentation
Annual conference of TSN, 2012
Taichung

Background

- Non-traumatic extremity amputation places a considerable burden on individuals, families, and health care finances.

Condition	2005	2006	2007	2008
Ischemic amputation				
Mean, $	51,952	55,521	55,527	55,311
Median, $	35,069	37,456	33,722	35,893
Total, $	59,849,292	61,684,119	56,470,502	56,528,330
Hospitalizations, n	1,152	1,111	1,017	1,022
Coronary heart disease[b]				
Mean, $	43,280	40,412	41,924	40,999
Median, $	34,954	33,027	34,213	33,321
Total, $	1,108,671,561	991,833,792	924,145,457	876,268,816
Hospitalizations, n	25,616	24,543	22,043	21,373
Stroke and transient ischemic attack[c]				
Mean, $	29,008	27,706	29,361	29,709
Median, $	18,173	16,917	17,921	17,831
Total, $	351,641,640	336,098,550	338,327,622	349,819,464
Hospitalizations, n	12,122	12,131	11,523	11,775

Prev Chronic Dis 2011;8(6):A141

Background

Compared with the general population, dialysis patients

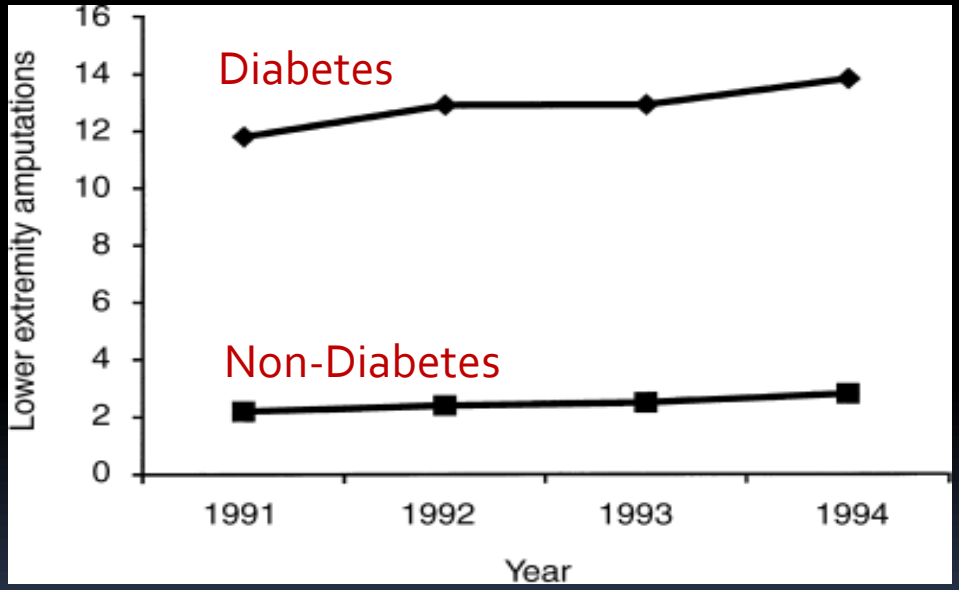
↑ amputation incidence ↑ post-amputation mortality rates.

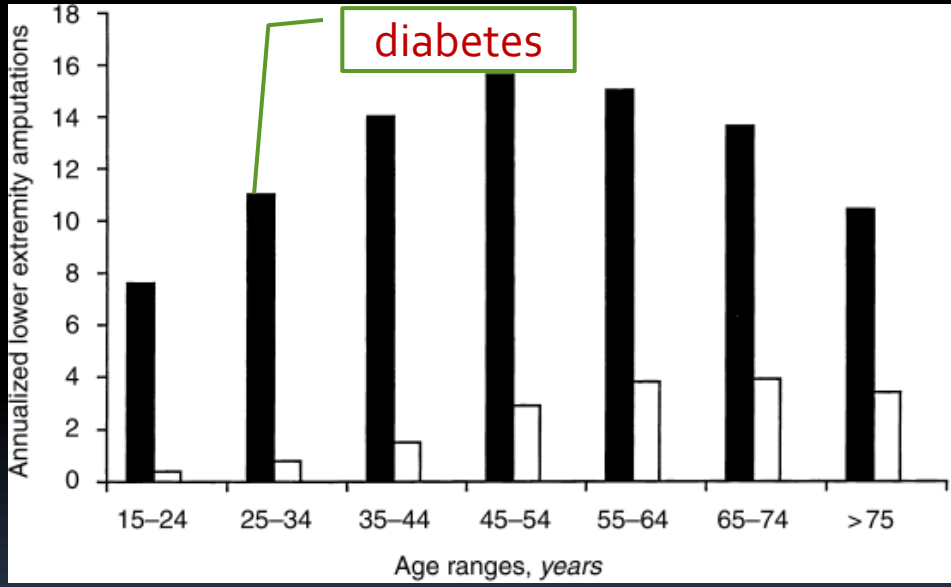
	Days postamputation						
	N	30	60	90	182	365	730
All persons	24,877	88.9%	80.1%	74.2%	62.8%	49.3%	32.7%
Age							
0 to 24	29	86.2	86.2	86.2	79.3	69.0	65.0
25 to 34	419	96.4	93.2	89.7	83.0	73.8	61.3
35 to 44	2,342	95.8	91.3	88.0	78.6	67.3	53.3
45 to 54	4,038	93.8	88.0	84.0	74.1	60.7	44.0
55 to 64	6,365	90.2	82.0	76.5	65.1	51.3	33.1
65 to 74	7,956	86.0	75.7	68.7	56.5	41.7	24.5
75 and over	3,324	80.4	66.3	57.0	43.9	30.9	15.8
Gender							
Male	13,339	89.4	81.1	75.7	64.9	51.5	35.0
Femlae	11,538	88.3	78.9	72.4	60.5	46.7	29.9
Race							
Asian	363	89.0	79.9	73.6	63.4	47.1	27.4
African American	8,287	90.0	81.9	76.3	66.6	54.1	37.3
Native American	553	93.1	85.9	80.8	70.9	59.7	39.1
Other/unknown	333	91.0	82.3	77.2	68.2	49.6	35.3
White	15,341	88.1	79.9	72.7	60.4	46.4	30.0
Primary diagnosis							
Diabetes	16,970	90.5	82.4	76.7	65.7	51.7	34.8
Glomerulonephritis	892	83.7	74.3	66.8	54.6	41.3	27.8
Hypertension	4,059	84.7	73.7	66.6	55.3	42.3	26.2
Cystic kidney disease	201	79.1	69.7	62.7	50.3	41.8	26.0
Interstitial nephritis	246	82.9	74.0	69.1	53.3	39.0	23.4
Obstructive nephritis	170	88.2	77.1	71.8	61.2	48.2	32.0
Other	363	84.6	75.2	70.5	55.4	44.9	29.2

Kid Int 1999; 56, 1524–1533

Background

- Diabetes is the strongest risk factor of amputation in dialysis patients.

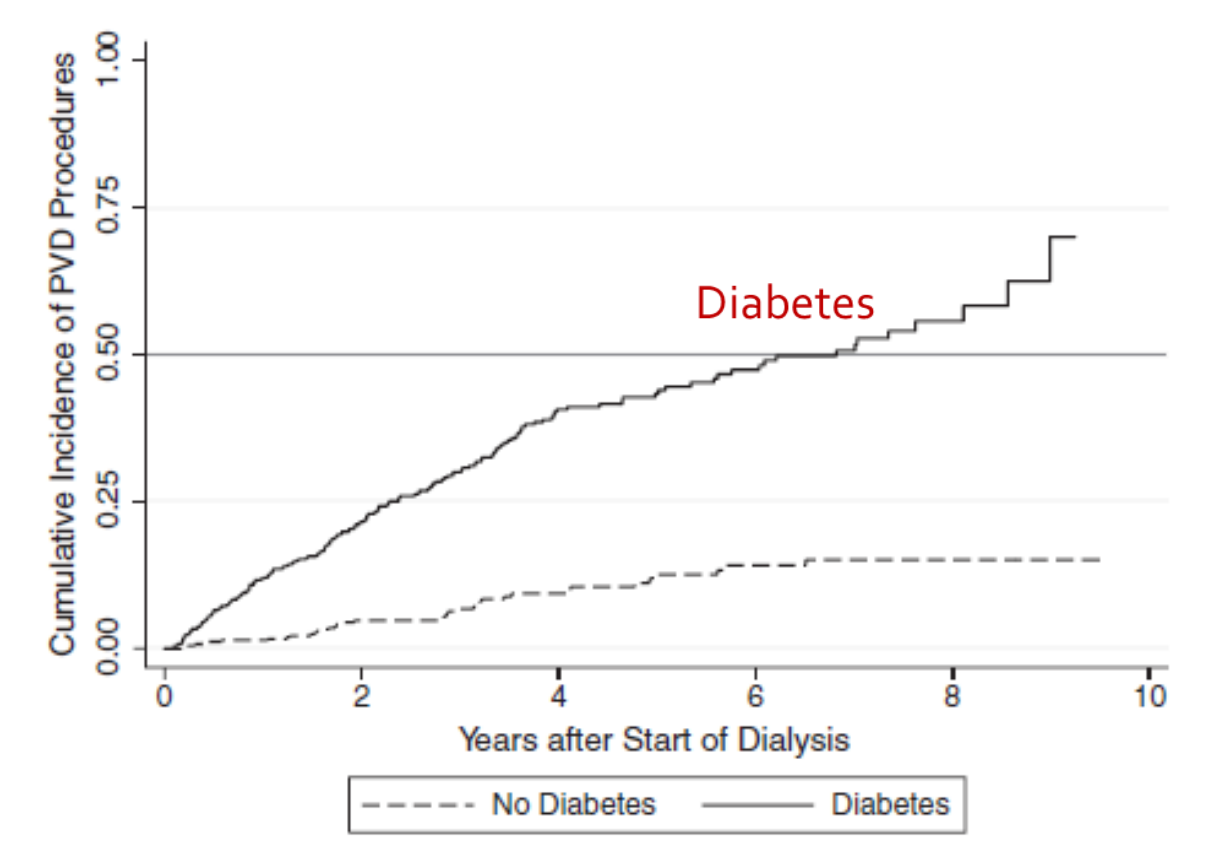




Kid Int 1999; 56, 1524–1533

Background

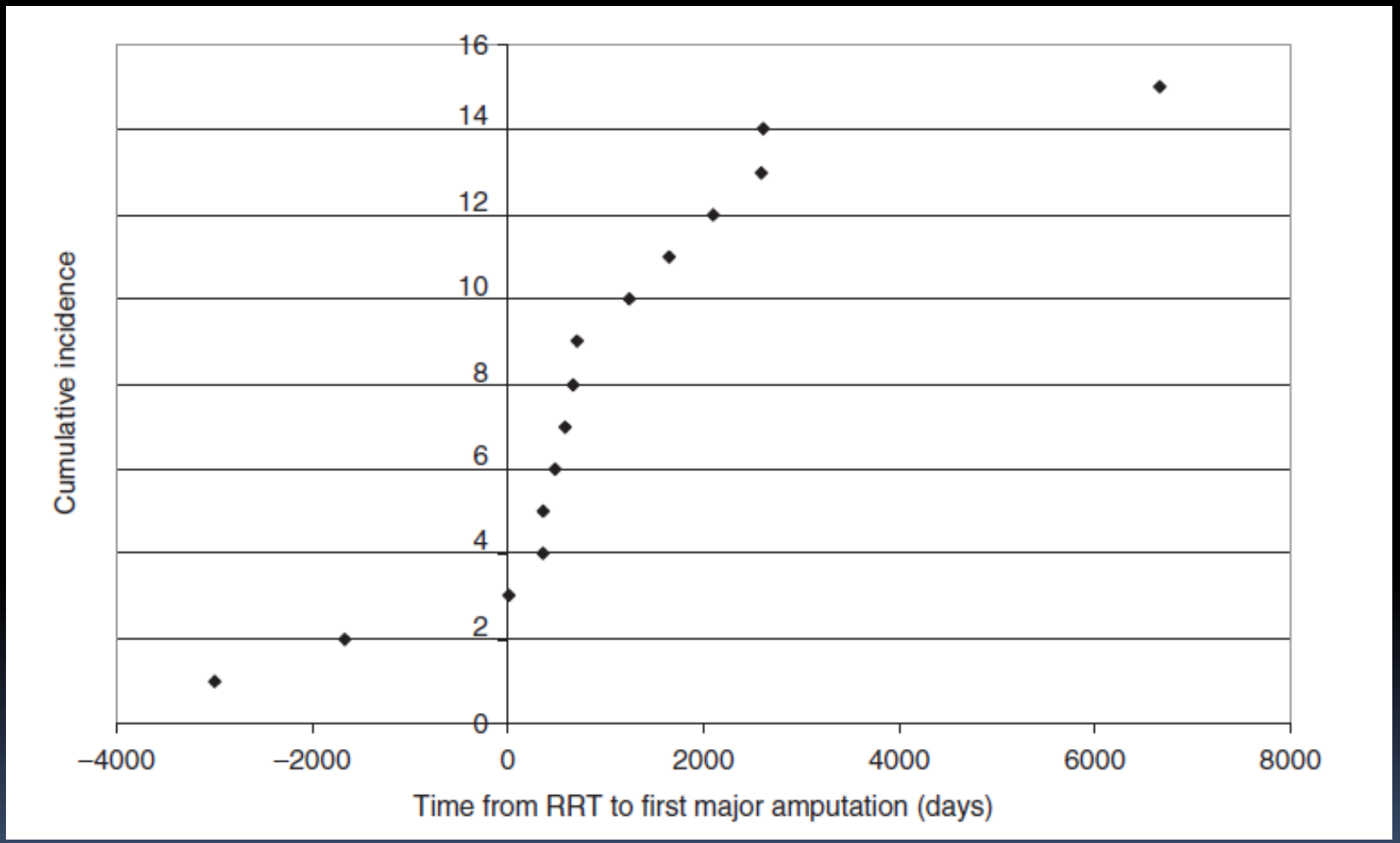
Cumulative incidence of PVD-related procedures after the start of dialysis, by baseline history of diabetes. P < 0.001 by log-rank test.



Clin J Am Soc Nephrol 2009;4: 1637–45.

Background

Recent commencement of dialysis is a recognized risk factor



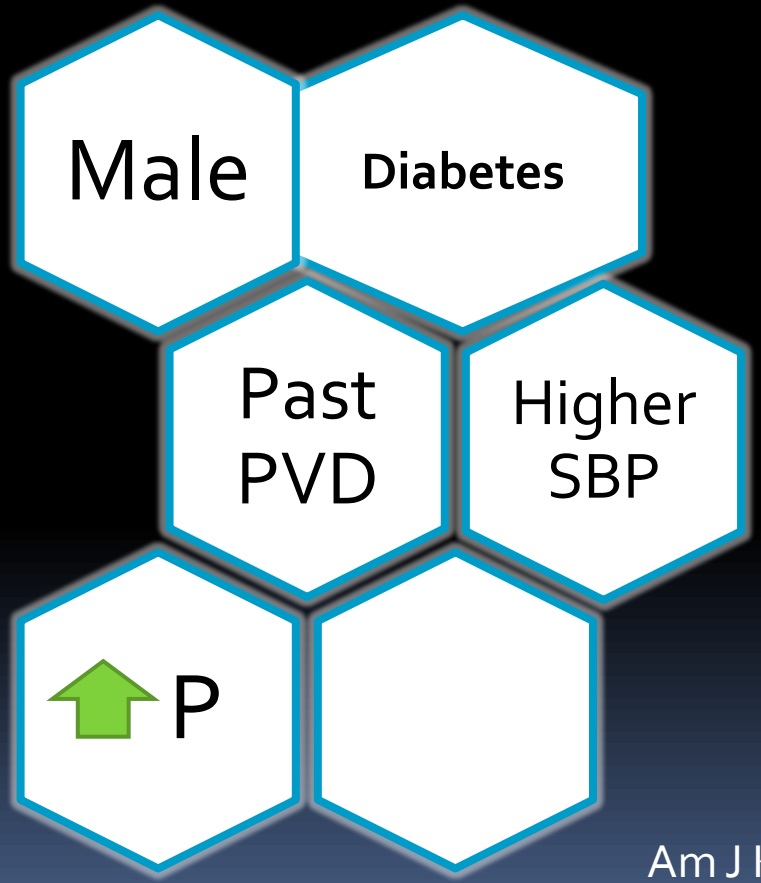
The Incidence risk of major amputation is 31.98 in the first year.

Game FL et al. NDT 2006;21:3207-3210

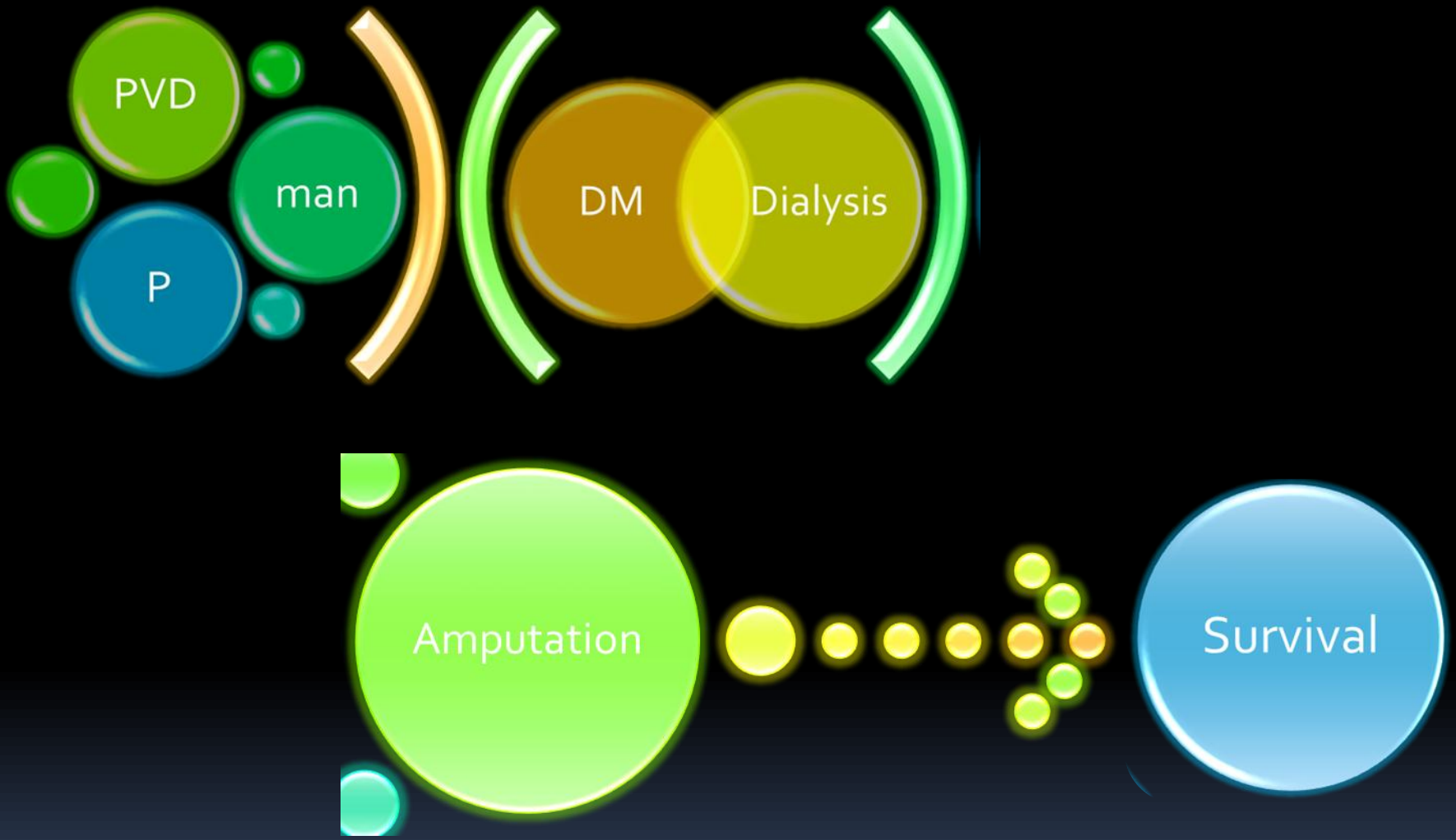
Background

From the Dialysis Morbidity and Mortality Study Waves 3 and 4

- Risk factors of amputation in hemodialysis patients



Am J Kidney Dis 2003; 41: 162–170



Risk factors of amputation in HD patients

Background

- Only a few studies have investigated the risk factors of amputation in PD patients, and these have had limited sample size
- Pliakogiannis et al , 71 diabetic PD patients

Clin Nephrol 2008, 69: 361-7

Background

- In the clinic, we noted that PD patients who required hypertonic peritoneal dialysis (HPD) solution soon after the initiation of PD were more likely to require amputation

Hypothesis

Early HPD use is related to future amputation in PD patients

Methods

- Extract a Longitudinal Health Insurance Database (LHID) from National Health Insurance Research Database (NHIRD) of the National Health Research Institute.

Methods

During 1998-2009

- Enrolled patients

  First diagnosed with ESRD (ICD-9-CM code 585) and receiving PD.

  HPD cohort: received HS (i.e., 7.5% icodextrin solution or 4.25% dextrose solution) within the first 6 months of initiating PD

  Comparison cohort: other new PD patients

Methods

- Excluded:

  (1) who underwent amputation before the index date

  (2) who registered ESRD but did not have record of PD

  (3) who had received HD or had undergone renal transplantation before the index date.

- We followed the cohorts until diagnosis and surgery for the first amputation (ICD-9-CM 785.4 and 440.24; ICD-9-CM 84.10-84.17) been made, withdrawal from insurance, loss to follow-up, or December 31, 2009.

Methods

- Baseline comorbidities analyzed
  - Diabetes (ICD-9 code 250)
  - Hypertension (ICD-9 codes 401-405)
  - Ischemic heart disease (ICD-9 codes 410-414, A270, and A279)
  - Previous foot ulcers (ICD-9 codes 707.1-707.9)
  - Diabetic neuropathy (ICD-9 codes 353.5, 357.2, 354.0-355.9, 337.1)
  - Peripheral vascular disease (PVD, ICD-9-CM codes 443.89 443.9)
  - Hyperparathyroidism (ICD-9-CM codes 252.0)
  - Heart failure (ICD-9-CM codes 428)
  - Diabetes duration
  - Dialysis vintage

	Comparison cohort N = 296 (%)	HPD cohort N = 203 (%)	p-values
Age, mean (SD) years	50.9 (17.0)	56.2 (15.8)	0.0005*
≦30	41 (13.9)	13 (6.4)	0.005
31-50	103 (34.8)	56 (27.6)	
51-70	108 (36.5)	94 (46.3)	
>70	44 (14.9)	40 (19.7)	
Sex			0.350
Female	170 (57.4)	108 (53.2)	
Male	126 (42.6)	95 (46.8)	
Comorbidity			
Hypertension	247 (83.4)	182 (89.7)	0.049
Ischemic heart disease	81 (27.4)	72 (35.5)	0.054
Diabetes	79 (26.7)	89 (43.8)	<0.0001
DM foot ulcer	5 (1.7)	5 (2.5)	0.545
DM neuropathy	13 (4.4)	20 (9.9)	0.016
Heart failure	61 (20.6)	63 (31.0)	0.008
Peripheral vascular disease	5 (1.7)	5 (2.5)	0.5445
Hyperparathyroidism	7 (2.4)	9 (4.4)	0.1976
Follow-up duration, mean (SD)	4.2 (2.9)	3.0 (2.8)	<0.0001*
DM duration, mean (SD)	8.5 (4.1)	9.1 (4.0)	0.308*
ESRD duration, mean (SD)	4.4 (2.9)	3.5 (2.9)	0.001*

Table 2:
Incidence of amputation and multivariate Cox proportional hazards regression analysis measured hazard ratio for PD patients using hypertonic solution

Patient group	Event	PYs	Rate	Crude HR (95% CI)	Adjusted HR (95% CI)
Comparison	10	1248	8.01	Ref	Ref
HPD	15	608	24.7	3.05(1.36-6.82)	2.48(1.06-5.82)**

PYs: person-years; rate: incidence rate, per 1000 person-years
HR: hazard ratio; CI: confidence interval
Model adjusted for age, sex, hypertension, ischemic heart disease, heart failure and diabetes

HPD cohort had a 2.48-fold increase in the HR of new amputation compared with comparison cohort

Table 3:
The interaction between diabetes and hypertonic solution for amputation risk

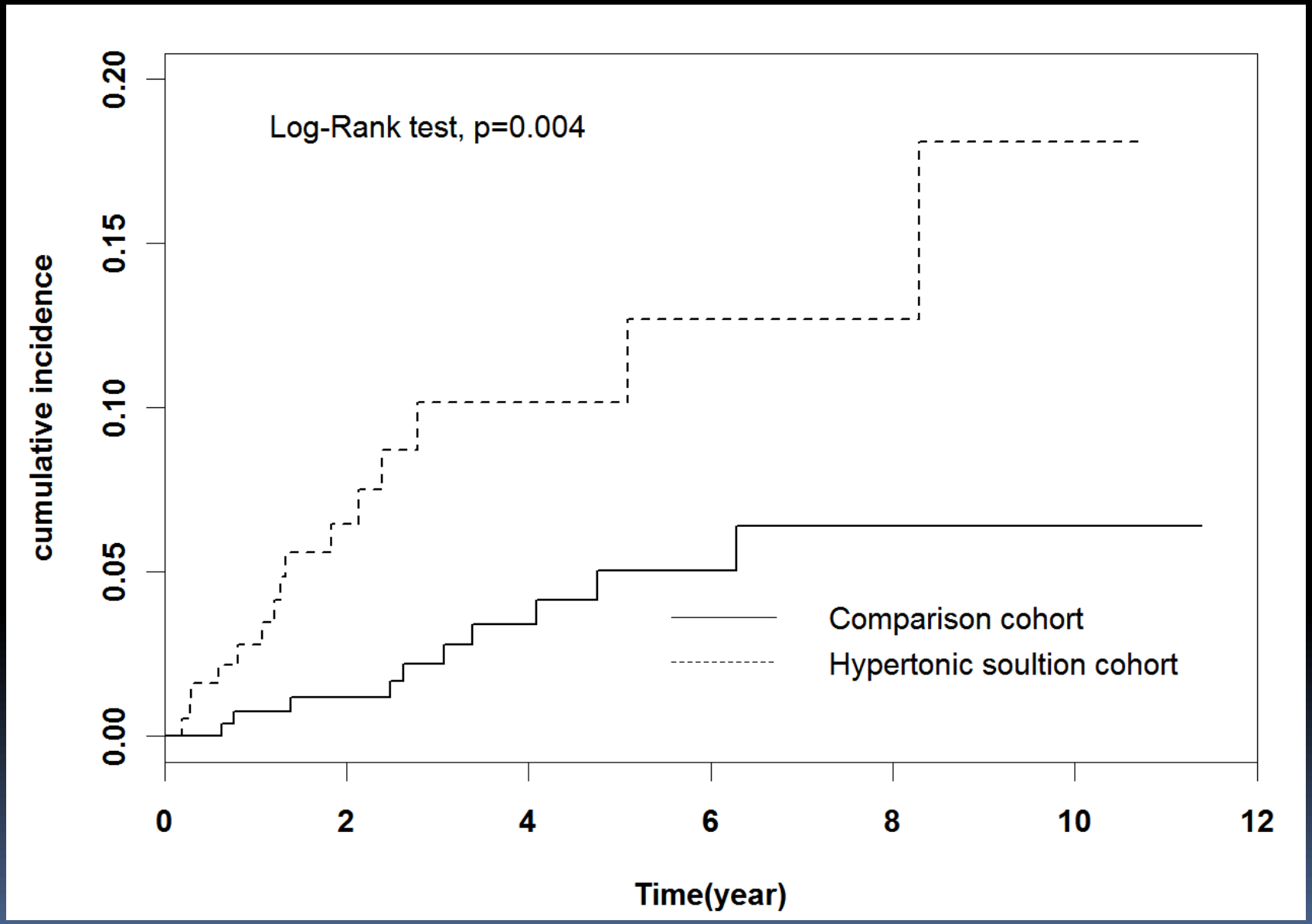
			Crude HR	Adjusted HR
HPD	Diabetes	Rate	HR (95%CI)	HR (95%CI)
No	No	0.97	Ref	Ref
No	Yes	40.6	44.09(5.50-353.4)	19.45(2.32-162.79)*
Yes	No	4.70	4.92(0.45-54.37)	3.57(0.32-39.72)
Yes	Yes	71.1	80.67(10.3-631.61)	45.67(5.67-367.75)*

Rate: incidence rate, per 1000 person-years
HR: hazard ratio; CI: confidence interval
Model adjusted for age, sex, hypertension, heart failure and ischemic heart disease
p value for interaction > 0.05

HPD cohort who had concomitant DM carried the highest risk, with 45.67 times the incidence of amputation in non-HPD non-diabetic patients.

Figure1

Cumulative incidence of amputation in hypertonic solution cohort and comparison cohort



Discussion

- Recent commencement of dialysis therapy has been recognized as an influential risk factor for lower limb amputation in the DM population

Diabetes Care 2000, 23: 432-3.

Discussion

- Several researchers have studied the pathophysiological changes that occur during hemodialysis, which may contribute to these limb-threatening conditions.
- Systemic hypoxemia, microcirculatory hypoperfusion, and decreased transcutaneous oxygen tension of the lower limbs can occur during and after HD; all these factors could lead to limb ischemia and amputation

Aurigemma NM e al. NEJM 1977, 297: 871-73.
Bemelmans RHH et al.NDT 2009, 24: 3487-92.
Hinchliffe RJ et al. NDT 2006, 21: 1981-3.

Discussion

- Although there are no comparable data on PD, it is possible that HPD could produce similar effects.
- HPD might create a more rapid fluid shift into the peritoneal cavity, reducing microcirculatory blood flow and tissue oxygen tension.
- PD patients placed on HPD have clinical signs of fluid overload, such as hypertension and tissue edema, which may worsen tissue oxygenation status.

Discussion

- Li et al found that PD patients have higher incidence rates of mesenteric ischemia than HD patients, indicating that PD therapy might contribute to the advancement of microvascular disease

Li et al. Am J Nephrol 2012; 35: 491-7

Discussion the strengths of this study

- The NHIRD database providing complete data about the incidence of amputation ,age, sex, types of dialysis solution, dialysis vintage, and comorbidities.

Discussion the strengths of this study

- We excluded subjects with previous amputations.

- Excluding patients with past amputation might eliminate possible bias with regard to analyzing future amputation and provide a clearer interpretation of the effect of HPD on limb ischemia.

Discussion the limitations of this study

- The number of subjects was relatively small, leading to large confidence intervals.

Discussion the limitations of this study

- It is possible that some patients had subclinical PVD.
- However, we also considered co-morbidities such as foot ulcers, heart failure, and cardiovascular risk factors associated with PVD, suggesting that any effect of undiagnosed PVD on our results was likely to be subtle.

Discussion the limitations of this study

- Lack precise information about smoking status and the calcium and phosphate levels, which might be associated with the risk of future amputation.
- However, Pliakogiannis et al reported that time average Kt/v, creatinine clearance, serum calcium levels, calcium and phosphate production, and intact parathyroid hormone level are not associated with amputation in PD patients

Clin Nephrol 2008, 69: 361-7

Discussion the limitations of this study

- We also lacked information about the subjects' scores on baseline measures of circulatory status, such as the ankle-brachial index (ABI)
- Given that ABI is not correlated with the severity of peripheral arterial disease among dialysis patients and would be falsely elevated by arterial calcification, it may be appropriate to overlook ABI in the current study.

Adragao T et al. NDT 2012, 27: 318-325.

Conclusion

- Along with diabetes, early utilization of HPD is associated with the subsequent risk of amputation in PD patients.
- We suggest that PD patients be provided intensive education on foot protection and screening for evidence of limb ischemia, especially those who received HPD early.

THANKS FOR YOUR ATTENTION