David C. Mendelssohn MD, FRCPC

DOPPS Update 2010

Budapest Nephrology School
August 30, 2010

Overview

1) General aspects of DOPPS
2) Facility based analysis
3) High hemoglobin
4) Coumadin use
5) Summary and conclusions

Dialysis Outcomes and Practice Patterns Study (DOPPS)

- DOPPS is supported by scientific research grants from Amgen (since 1996), Kyowa Hakko Kirin (since 1999, in Japan), Genzyme (since 2009), and Abbott (since 2009) without restrictions on publications

DOPPS

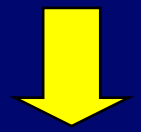
More than a decade of DOPPS

- Longitudinal observational study of HD patients and practices in 12 countries
- Conducted in four phases: I (1996-2001); II (2002-2004); III (2005 – 2008); DOPPS IV (currently ongoing)
- Represents ~ 70% of the global HD population
- Wide variety of data collected both from health care providers and patients
- Goal: Identify HD practice patterns associated with improved outcomes to improve patient longevity

Key Points

Ho: Large differences in survival between country & facilities partially due to variations in modifiable facility practices

Improvements in HD Practices



Improved Patient Survival

DOPPS

DOPPS:
A Facility Practice-Based Study

Patient Demographics

+

Patient Comorbidities

+

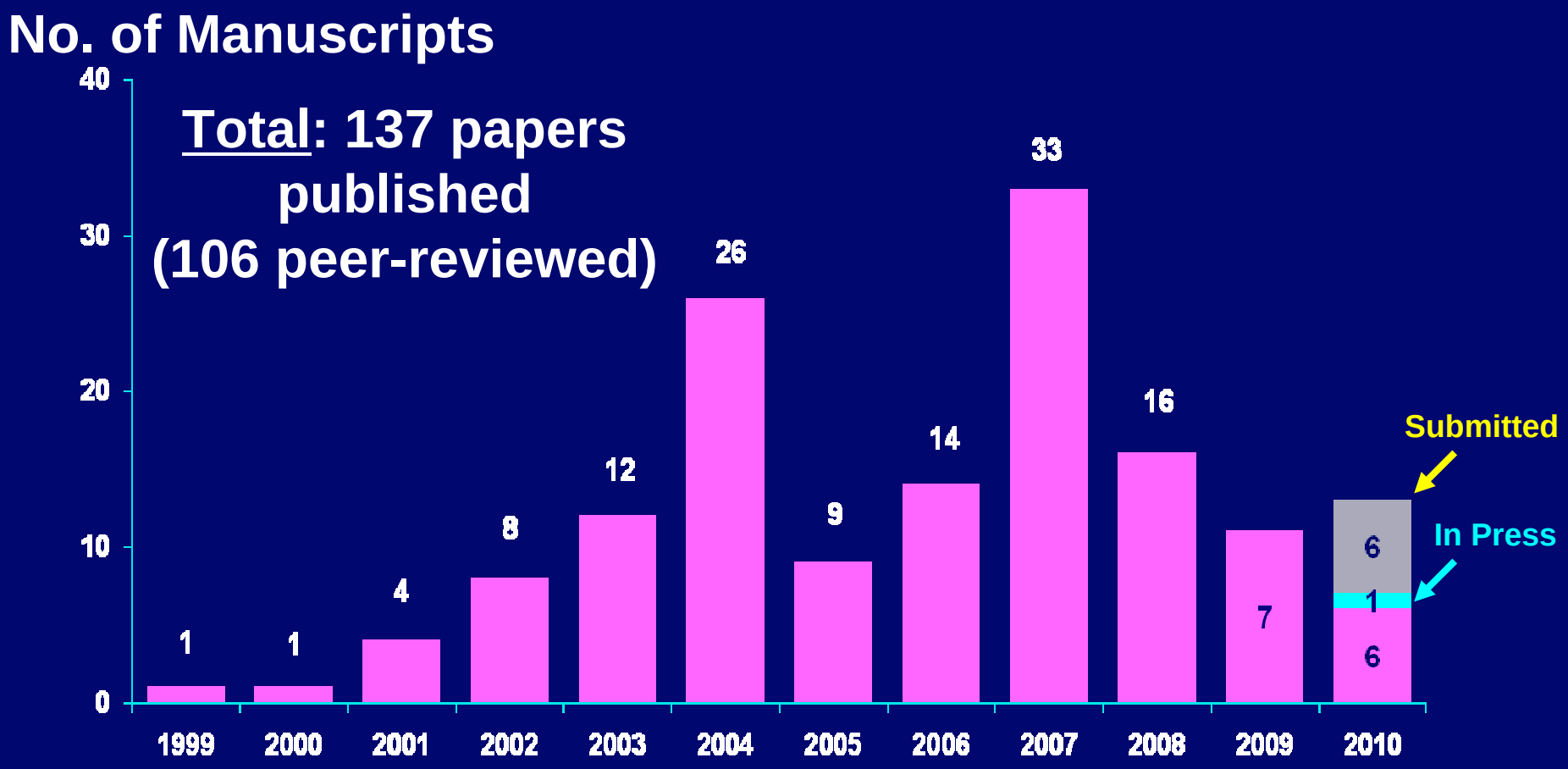
Practice Patterns

Patient Outcomes

- Mortality
- Hospitalization
- Vascular access
- Quality of life

Goal: Live longer – Live better!

DOPPS Impact: Annual Publication Totals, 1999-2010



As of 5/13/10 . Count for 2007 includes two special issues, ISHCOF (13 papers) and *J Nephrology Social Work* (6) ; 2004 count includes *AJKD* supplement (10 papers).

Table 1. Comparisons of Key Features Between Randomized Controlled Trials and Observational Studies

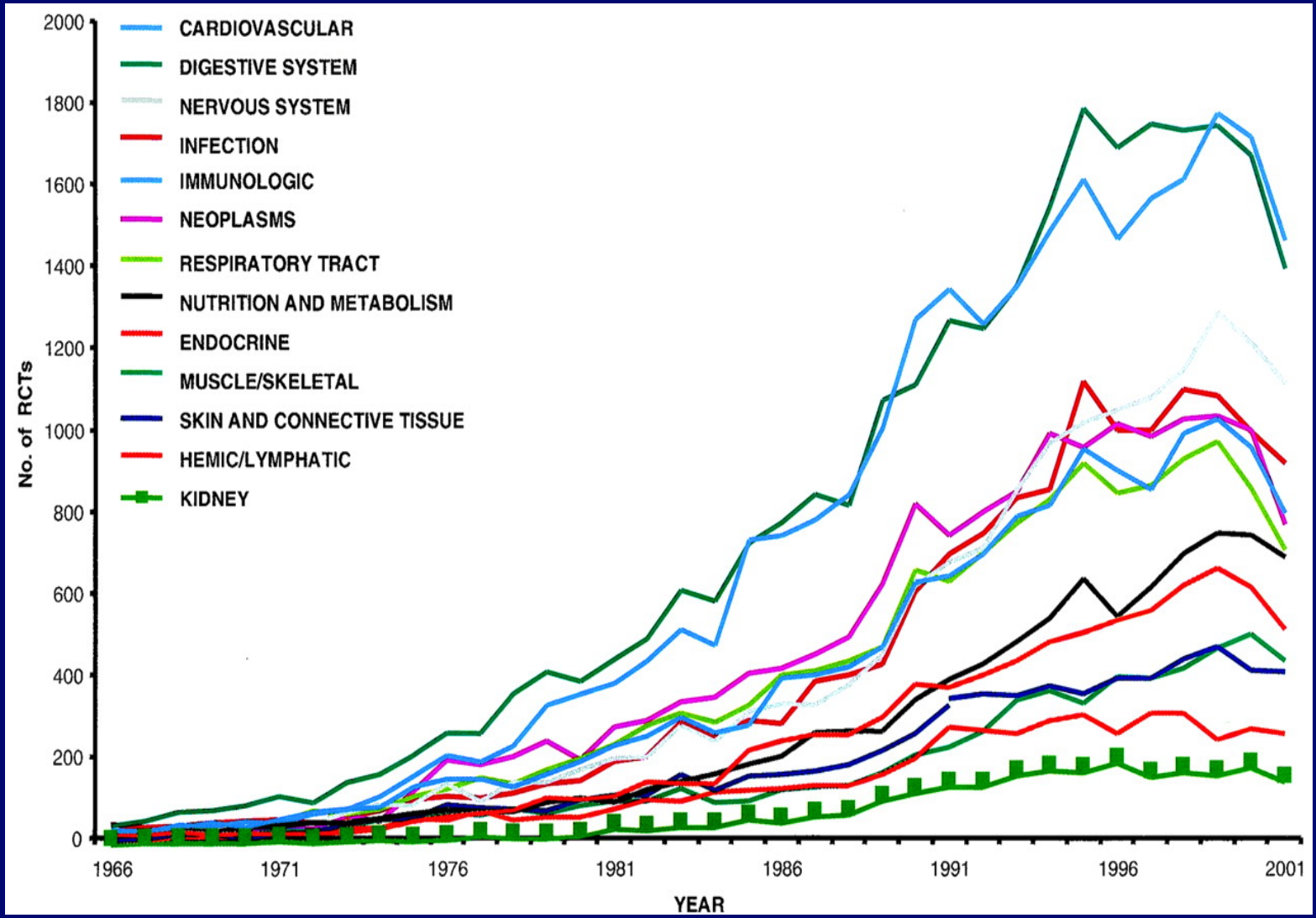
Feature	Controlled Trials	Observational Studies
Number of hypotheses	Usually only 1 or 2	Many
Cost per hypothesis	Very high	Low to moderate
Sample size	Often marginal	Less restricted
Study of poor treatment	Ethically not feasible	Feasible via representative sample study
Study of medications	Ideally suited	Confounding by indication*
Study of trends	Limited	Feasible
Causality	Yes (for positive findings)†	Correlation, suggestive only
Representativeness	Limits due to selection criteria	Feasible
Statistical adjustment	Usually not required	Always required

*Results showing benefit associated with medication use despite this confounding are of great interest

†Negative findings may be difficult to interpret because high cost usually limits the sample size

DOPPS

Port FK and Eknoyan G. *Am J Kidney Dis* 44:S1-S6, 2004



Strippolli et al, JASN 15: 411-419, 2004

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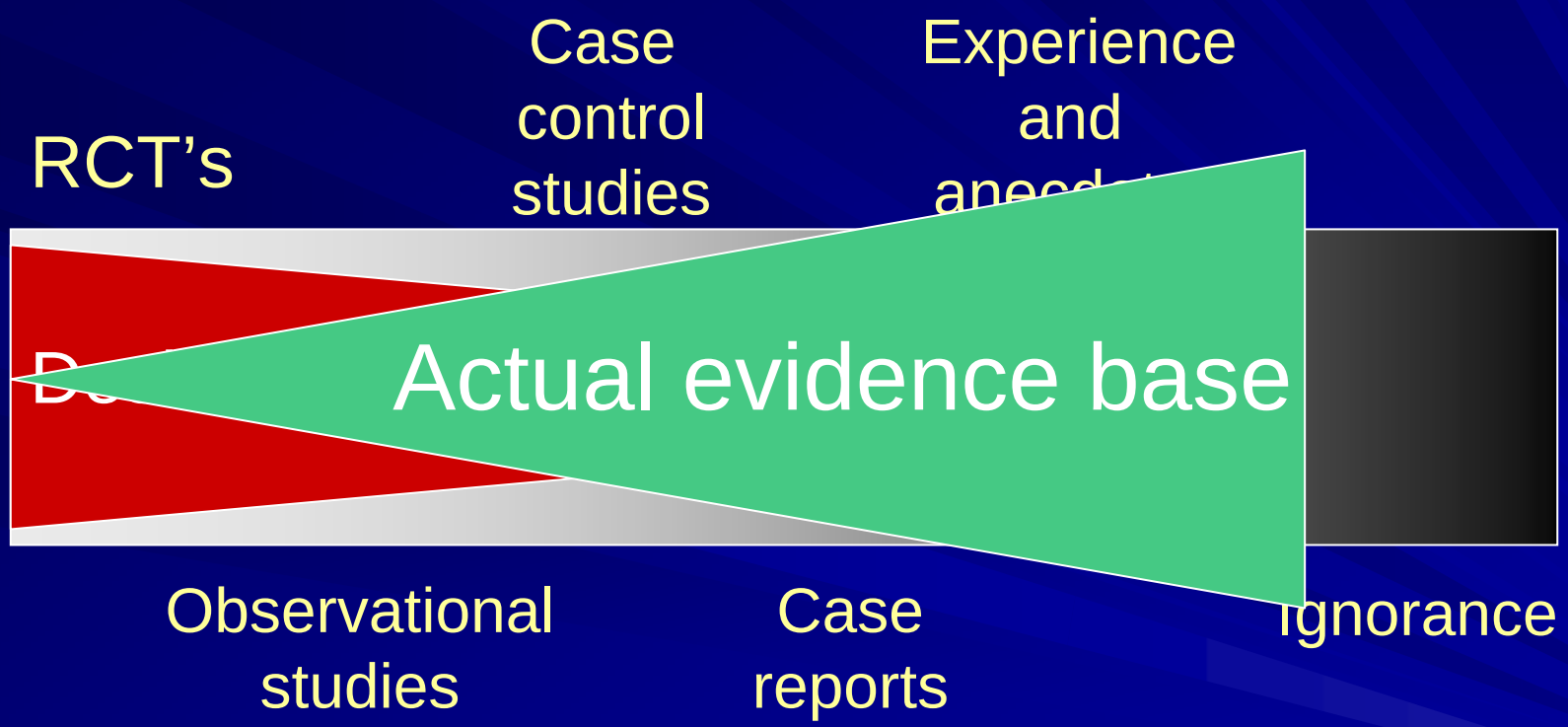
Nephrology's Dilemma



BMJ

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith and Jill P Pell

BMJ 2003;327;1459-1461

Individuals who insist that all interventions need to be validated by a randomised controlled trial need to come down to earth with a bump

Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

DOPPS

Can Principles of Randomization be Used in Observational Studies?

- Observational studies have problems with *Treatment by Indication Bias*
  - e.g. treatment is given to sicker patient and sicker patients have higher risk of death
- DOPPS observes large differences in practice patterns
  - e.g. 20% vs. 80% of patients on Vitamin D

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Can Principles of Randomization be Used in Observation Studies?

- When the average treatment patterns differ substantially among facilities (adjusted for case mix), this may be due to physician preferences
- Patients usually select dialysis facilities by factors independent of their own medical condition – e.g. by proximity from home
- Patients may be “assigned quasi-randomly” to the treatment preferences of their facility

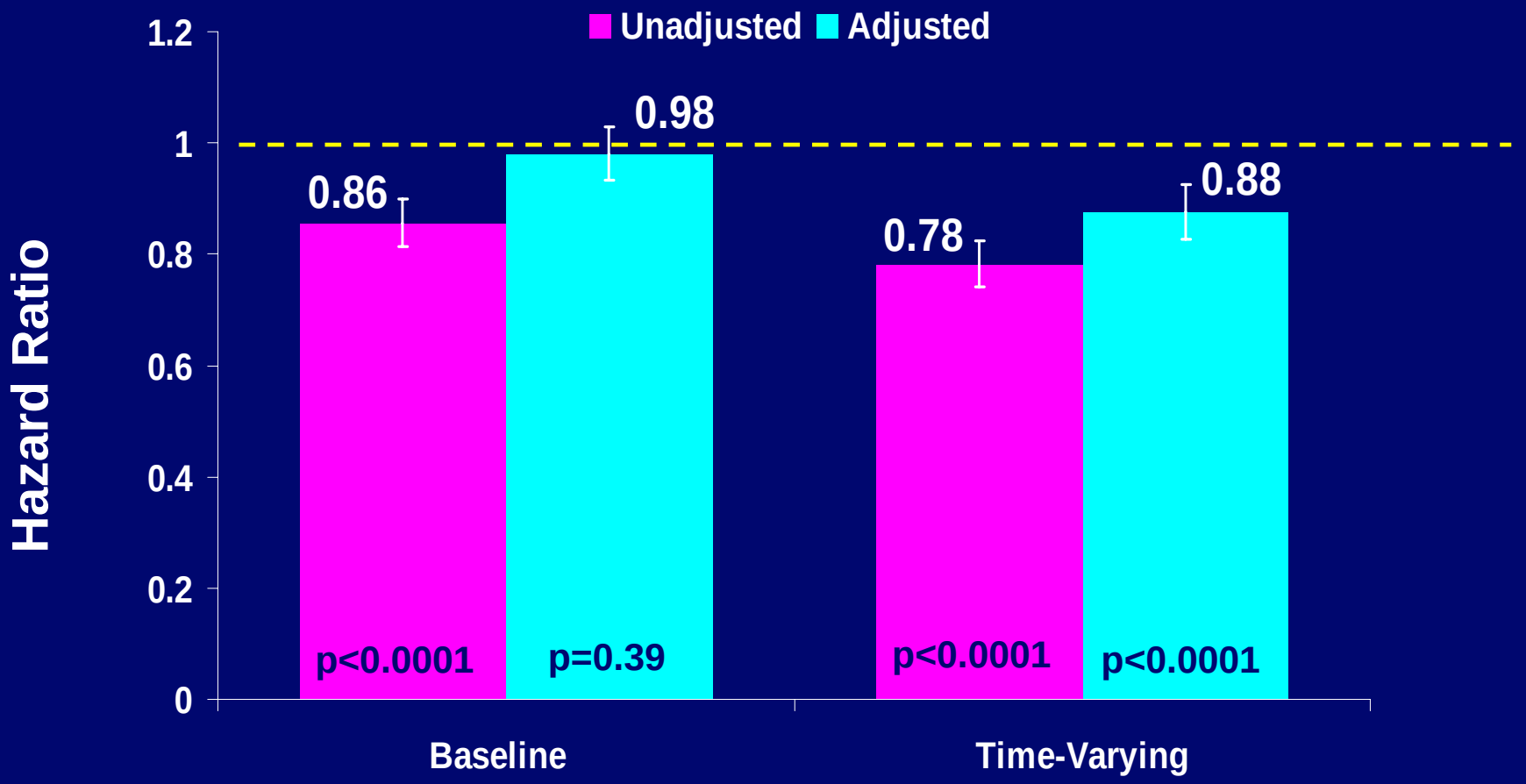
DOPPS

Facility-Level Analyses

- We assign the practice (e.g. % of patients on treatment X), not the treatment received, and use patient-level outcomes and adjust for both patient-level characteristics and other facility-level practices
- These models are *not* subject to the limitations of many ecologic analyses
- Despite advantages of our practice pattern approach, causality cannot be proven

DOPPS

Patients Prescribed Vitamin D Have Lower Mortality?



DOPPS I, II, and III (n=38,066). In time-varying model, vitamin D prescription was updated at each reporting interval. Adjusted models account for age, gender, race, years on ESRD, year of study enrollment, diabetes, catheter use, 14 summary comorbid conditions, calcium, phosphorus, iPTH, dialysate calcium, albumin, hemoglobin, and facility clustering, and are stratified by region.

Tentori et al. NDT 24; 963-972: 2008

Baseline Patient Characteristics

Characteristic	No Vit D (n=3,194)	Vit D (n=4,096)
Age (years)	61.5	60.7**
Male (%)	55.2	54.4
Black race (%)	27.4	41.2**
Years with ESRD	1.6	2.9**
AV Fistula (%)	19.7	28.1**
Graft (%)	31.8	42.9**
Catheter (%)	48.5	29.0**
Cerebrovascular Disease (%)	19.7	18.0

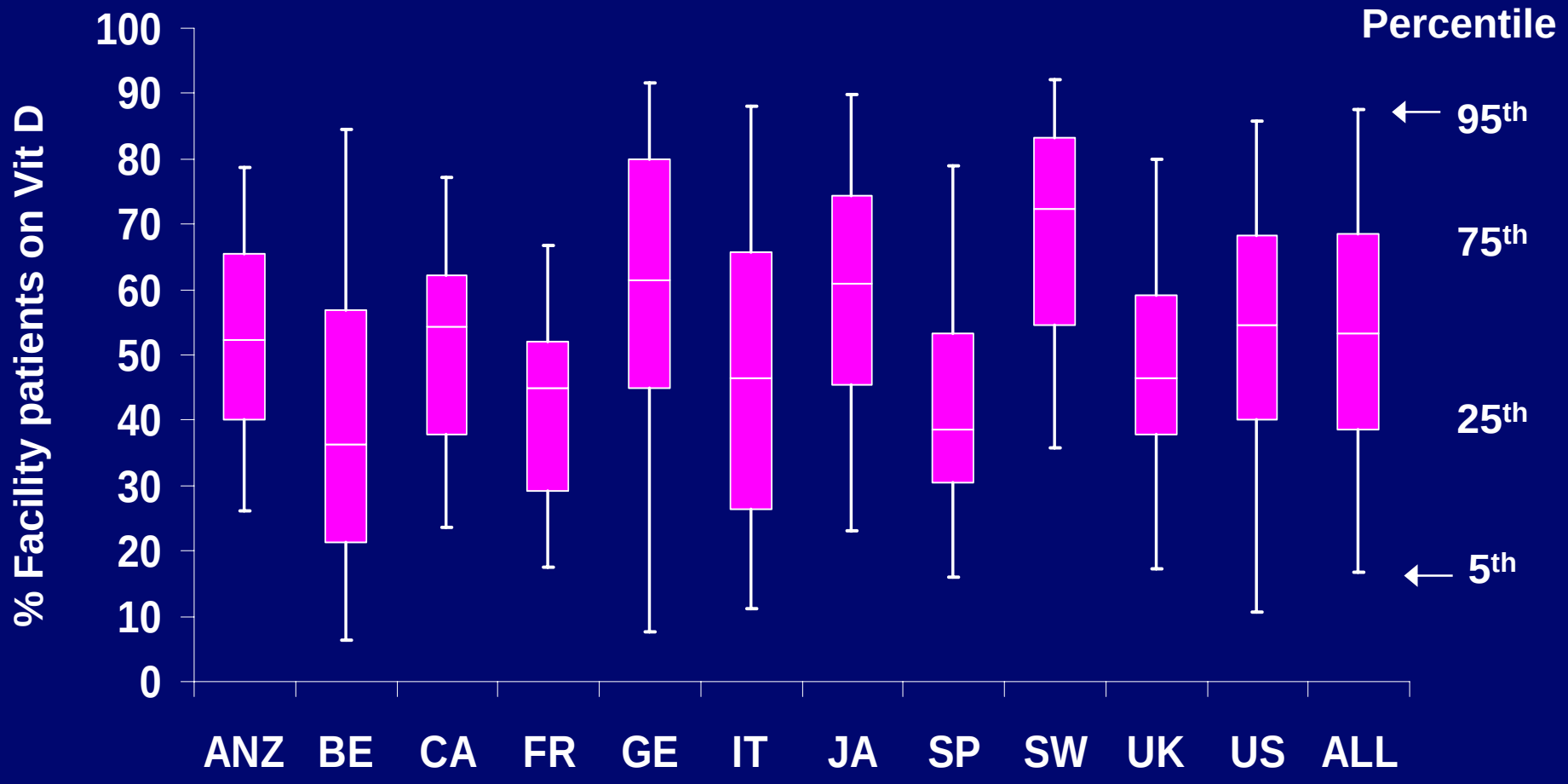
Characteristic	No Vit D (n=3,194)	Vit D (n=4,096)
CHF (%)	46.7	45.5
Hypertension (%)	84.3	87.1**
Lung disease (%)	15.4	13.4**
Psych disorder (%)	27.9	23.5**
PVD (%)	29.4	26.6**
Prior parathyroidectomy (%)	1.7	3.3**

Patients treated with Vitamin D have characteristics that are associated with lower mortality.

Other non-significant covariates tested: CAD, cancer, diabetes, and recurrent cellulitis

*p<0.05, **p<0.01 Initial cross-section of US patients in DOPPS I, II, III

Vitamin D* Prescription Varies Widely Among Facilities, by Country



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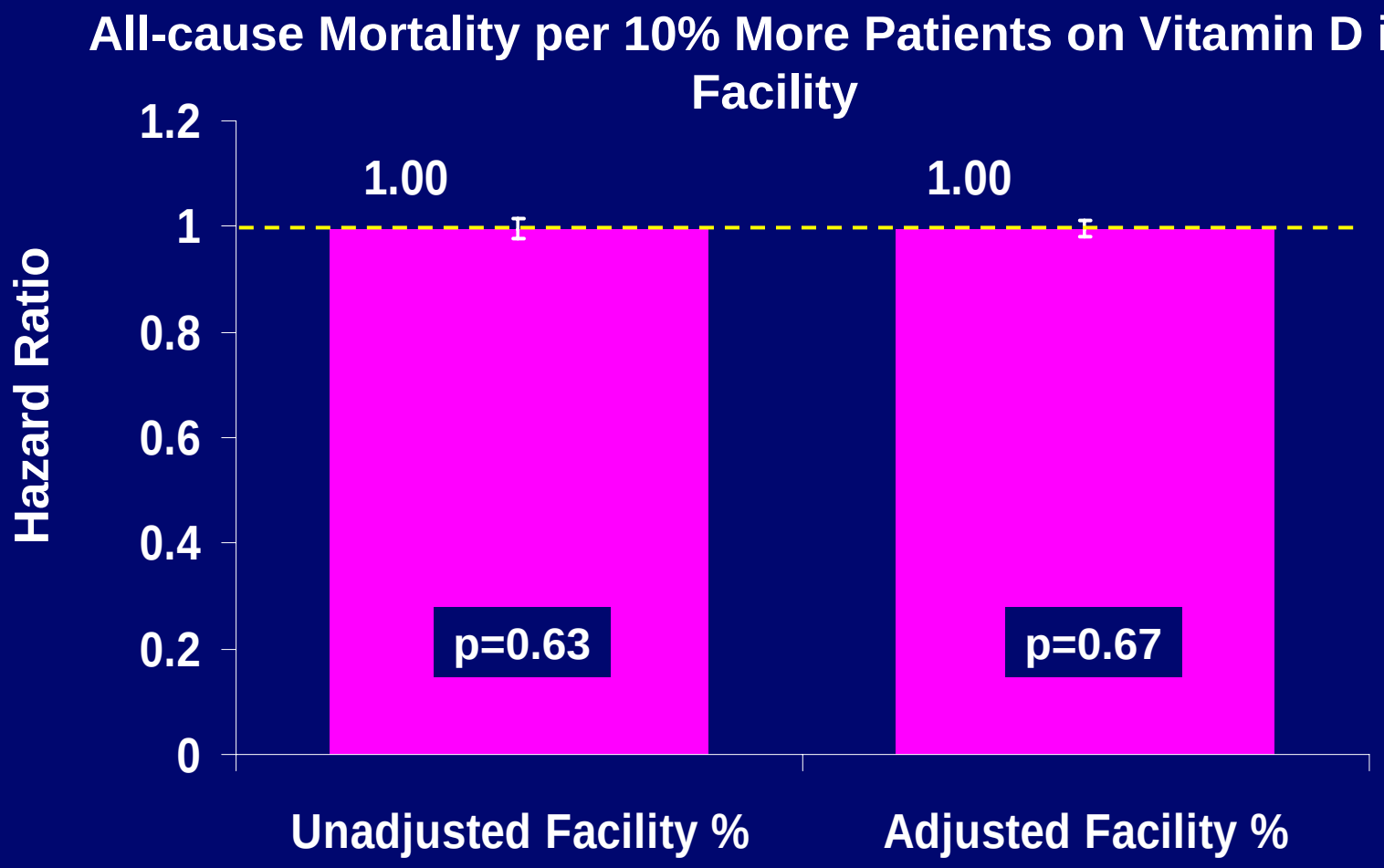
* Intravenous or oral vitamin D. DOPPS I, II, and III.

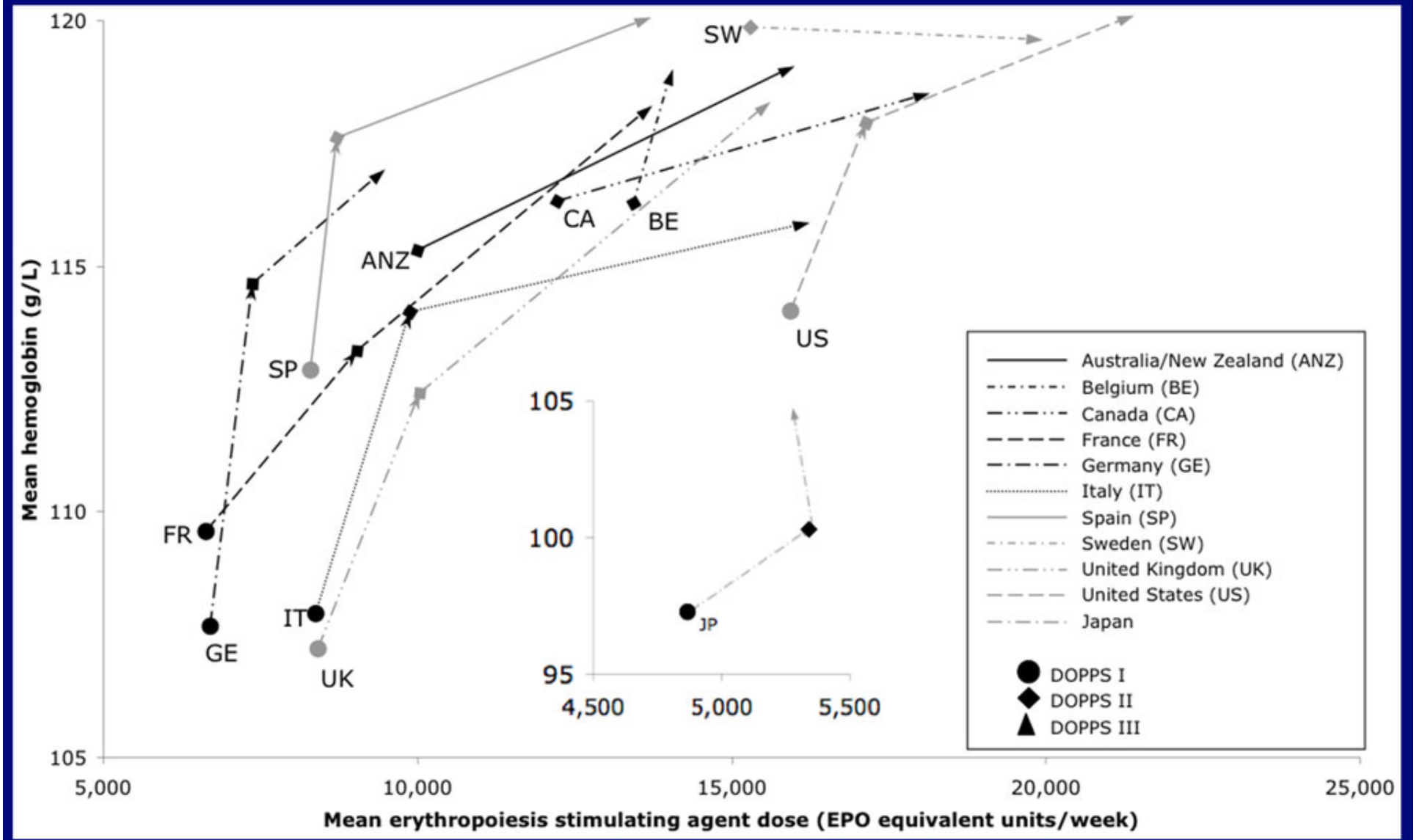
Patients in Facilities Prescribing More Vitamin D Have No Survival Advantage



DOPPS I, II, and III. Adjusted for age, gender, race, years on ESRD, year of study enrollment, diabetes, catheter use, 14 summary comorbid conditions, calcium, phosphorus, iPTH, dialysate calcium, albumin, and hemoglobin, are stratified by region and account for facility clustering.


PHILOSOPHY 101
OOPS...
PLATO
PLATO
PLAY-DOUGH
PLATO
MARK PARISI

Figure 1: Mean ESA dose and Hgb level



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McFarlane PA et al. *KI* 78: 215-223, 2010

Conclusions

- Both ESA usage and hemoglobin levels rose significantly in all but one of the 12 countries
- Clinicians have increased ESA doses and achieved higher hemoglobin levels as part of a broad international trend independent of the manner of ESA reimbursement
- Further studies are needed to define the factors that drive medical decision-making and facility policy related to anemia management

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McFarlane PA et al. *KI* 78: 215-223, 2010

The First International DOPPS Annual Report

www.DOPPS.org/AnnualReport

- Over a decade of longitudinal DOPPS data
- Multiple, representative cross-sectional cohorts
- Portrays country-specific results, trends in demographics, comorbidities, labs, and medication use

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Dialysis Outcomes and Practice Patterns Study

Hemodialysis Patients Who Maintain Higher Hemoglobin Concentration without ESA Treatment

David A Goodkin[1], Jennifer L Bragg-Gresham[1], Bruce Robinson[1], Christian Combe[2], Richard Fluck[3], David Mendelssohn[4], Tadao Akizawa[5], Ronald L Pisoni[1] and Friedrich K Port[1]

[1]Arbor Research, Ann Arbor, MI, United States; [2]Centre Hosp Univ de Bordeaux, France; [3]Derby City Gen Hosp, United Kingdom; [4]Univ of Toronto, Canada and [5]Showa Univ Sch of Med, Tokyo, Japan.

(manuscript in preparation)

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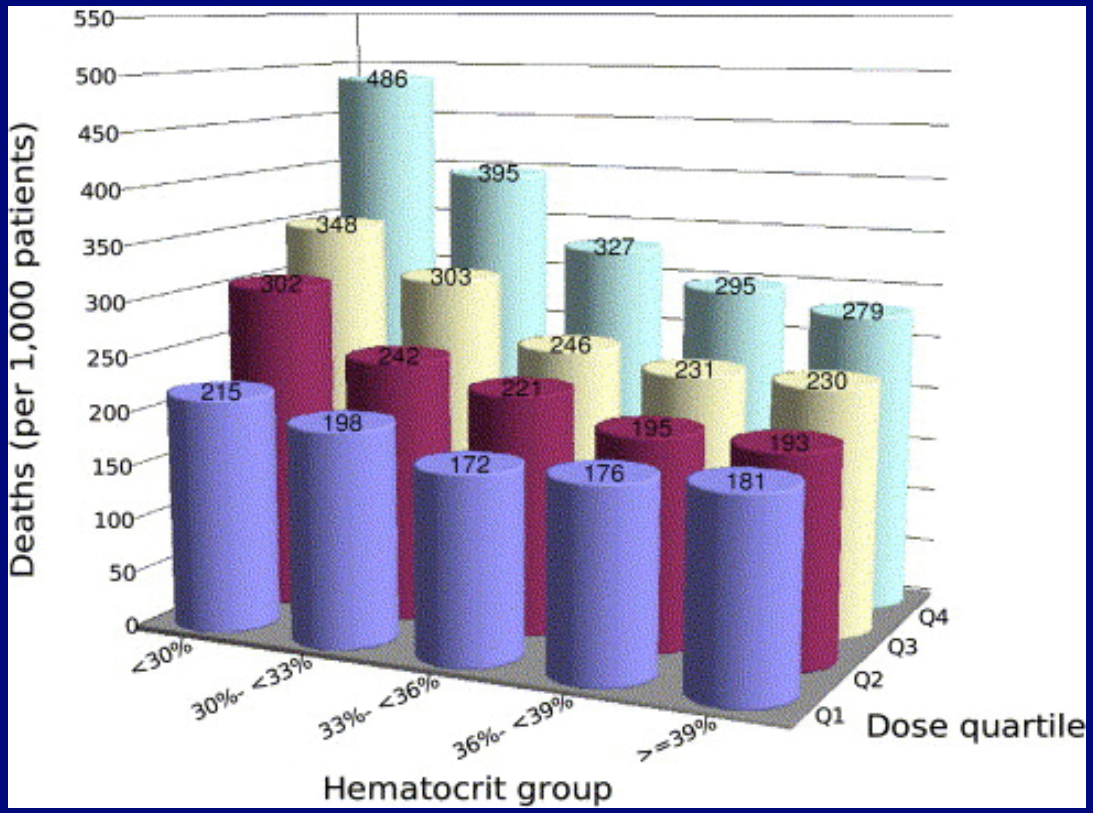
Epoetin requirements predict mortality in HD patients



In contrast to conventional wisdom, this study suggests that epoetin dosing requirements could provide important prognostic information beyond that predicted by hematocrit alone.

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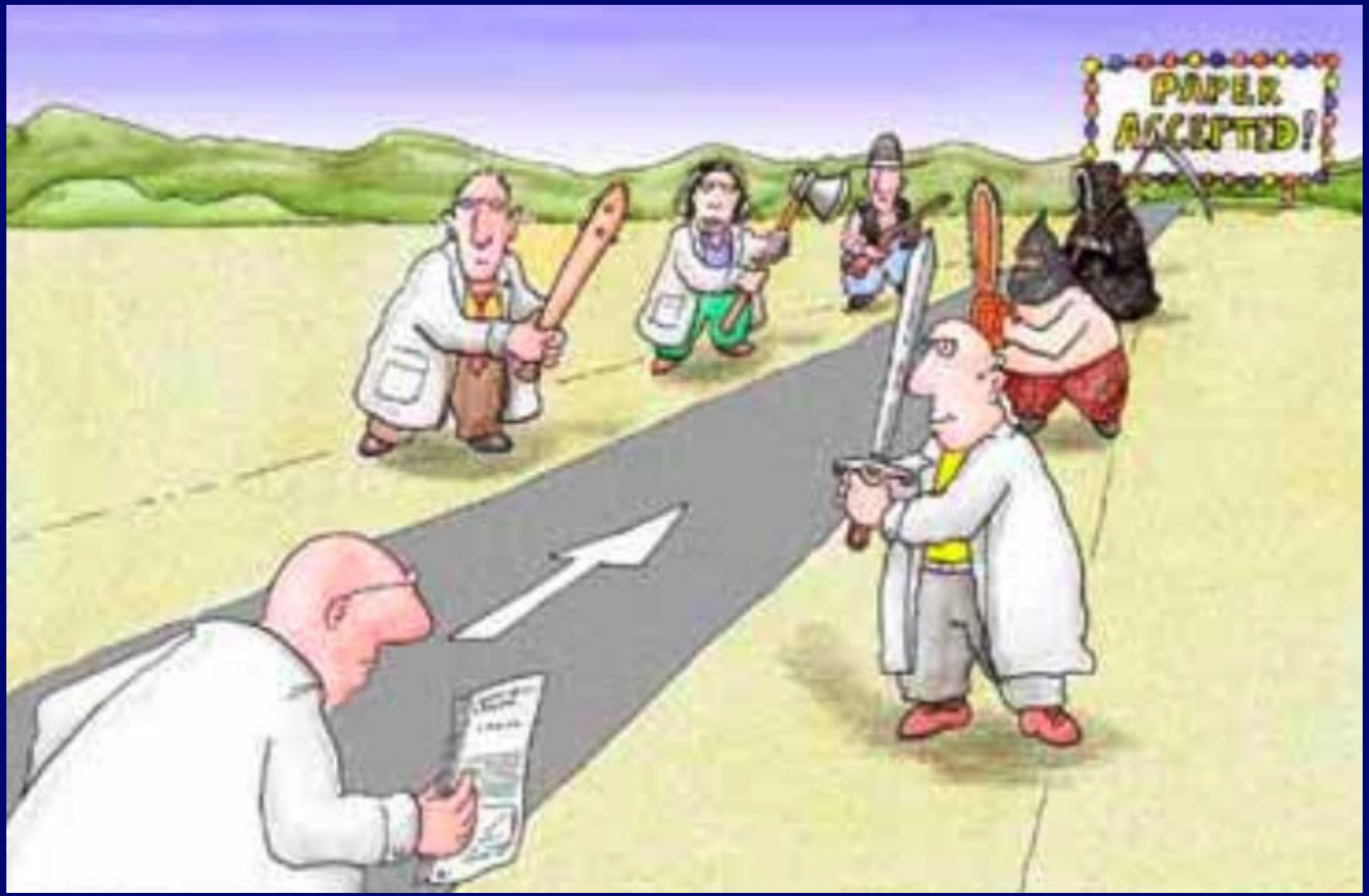
Zhang, Y et al. AJKD 44; 868-876: 2004.


PAPER ACCEPTED!

Anticoagulation and atrial fibrillation

Anticoagulation in ESRD

- Indicated for treatment and prevention of thrombosis, embolism and atrial fibrillation in the general population
- Few if any studies support the benefits of such therapy in dialysis patients
  - Yet, 30% take aspirin
  - Up to 25% take coumadin, but 4 studies demonstrate no benefit in preventing thrmbosis on HD access
  - A number of small studies suggest harm

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CLINICAL EPIDEMIOLOGY www.jasn.org

Anticoagulant and Antiplatelet Usage Associates with Mortality among Hemodialysis Patients

Kevin E. Chan,* J. Michael Lazarus,* Ravi Thadhani,† and Raymond M. Hakim*

*Fresenius Medical Care NA, Waltham, Massachusetts and †Nephrology Division, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts

ABSTRACT

Many prescribe anticoagulants and antiplatelet medications to prevent thromboembolic events and access thrombosis in dialysis patients despite limited evidence of their efficacy in this population. This retrospective cohort study examined whether use of warfarin, clopidogrel, and/or aspirin affected survival in 41,425 incident hemodialysis patients during 5 yr of follow-up. The prescription frequencies for warfarin, clopidogrel, and aspirin were 8.3, 10.0, and 30.4%, respectively, during the first 90 d of initiating chronic hemodialysis. Compared with the 24,740 patients receiving none of these medications, Cox proportional hazards analysis suggested that exposure to these medications was associated with increased risk for mortality (warfarin hazard ratio [HR] 1.27 [95% confidence interval (CI) 1.18 to 1.37]; clopidogrel HR 1.24 [95% CI 1.13 to 1.35]; and aspirin HR 1.06 [95% CI 1.01 to 1.11]). The increased mortality associated with warfarin or clopidogrel use remained in stratified analyses. A covariate- and propensity-adjusted time-varying analysis, which accounted for longitudinal changes in prescription, produced similar results. In addition, matching for treatment facility and attending physician revealed similar associations between prescription and mortality. We conclude that warfarin, aspirin, or clopidogrel prescription is associated with higher mortality among hemodialysis patients. Given the possibility of confounding by indication, randomized trials are needed to determine definitively the risk and benefit of these medications.

J Am Soc Nephrol 20: 872–881, 2009. doi: 10.1681/ASN.2008080824

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FMCNA

- N = 41425
- 8.3% on coumadin, 10.0% on clopidogrel, 30.4% on ASA
- Control group = 24740 on none

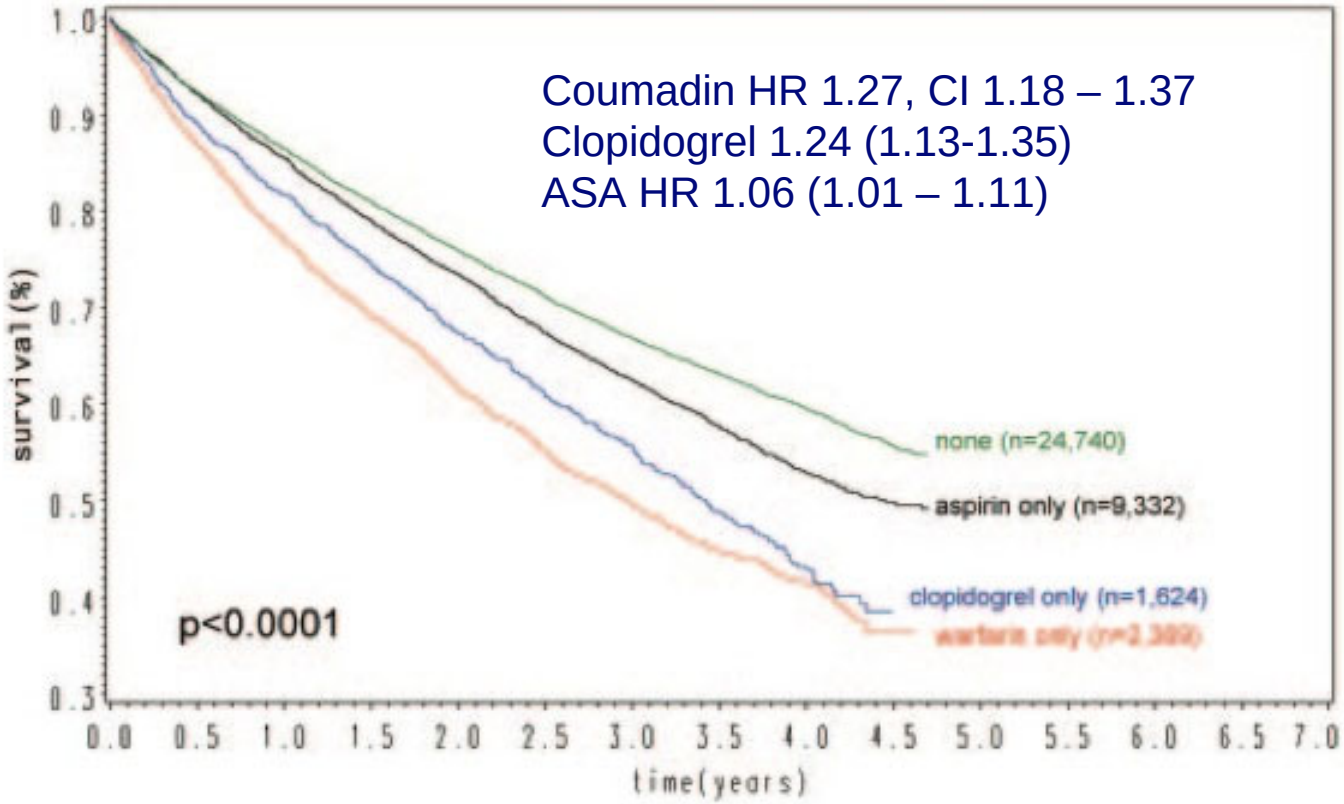

Figure 1. Kaplan-Meier analysis of survival by drug therapy. Log rank test among four groups was $P < 0.0001$. Pair-wise log rank test: Warfarin *versus* none ($P < 0.0001$), clopidogrel *versus* none ($P < 0.0001$), aspirin *versus* none ($P < 0.0001$).

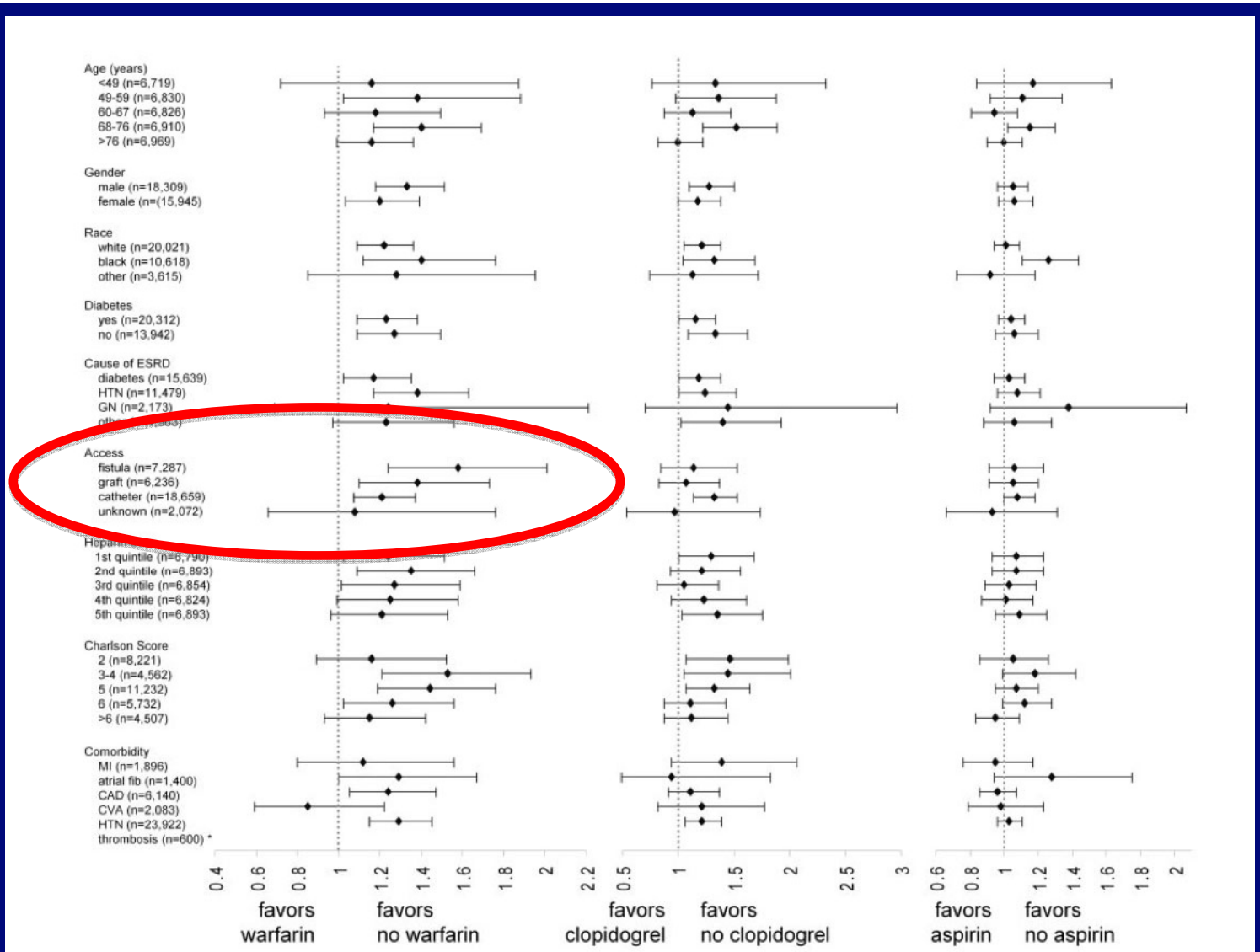

Figure 2. Mortality HRs by different drug therapy, stratified according to the characteristics of the patient. *Mortality HRs in patients with a history of thrombosis (n = 600): HR for warfarin (*versus* no warfarin) 1.28 (95% CI 0.81 to 2.04); HR for clopidogrel (*versus* no clopidogrel) 0.78 (95% CI 0.41 to 1.48); HR for aspirin (*versus* no aspirin) 1.39 (95% CI 0.75 to 2.59). All models are adjusted for age, race, gender, Charlson comorbidity index, entry date, dialysis access, cardiovascular drug use, body mass index, baseline laboratory values (hemoglobin, albumin, calcium, phosphorus, parathyroid hormone, creatinine, white blood cell count, and ferritin), dialysate calcium, heparin dosage, and propensity score with stratification for the facility SMR.

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Atrial Fib in ESRD (UpToDate accessed Feb. 16, 2010, last update August 2009)

- Most clinicians have been reluctant to administer prophylactic anticoagulation therapy for chronic AF in dialysis patients. Furthermore, the benefits versus risks have not been accurately determined.
- Thromboembolic risk is increased, but so is bleeding risk.
- It is reasonable to consider warfarin in those with low risk of bleeding and additional risk factors for thromboembolism (eg. CHF, prior TE), like in non-dialysis patients.

CLINICAL EPIDEMIOLOGY www.jasn.org

Warfarin Use Associates with Increased Risk for Stroke in Hemodialysis Patients with Atrial Fibrillation

Kevin E. Chan,* J. Michael Lazarus,* Ravi Thadhani,† and Raymond M. Hakim*

*Fresenius Medical Care NA, Waltham, Massachusetts; and †Nephrology Division, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts

ABSTRACT

Use of warfarin, clopidogrel, or aspirin associates with mortality among patients with ESRD, but the risk-benefit ratio may depend on underlying comorbidities. Here, we investigated the association between these medications and new stroke, mortality, and hospitalization in a retrospective cohort analysis of 1671 incident hemodialysis patients with preexisting atrial fibrillation. We followed patient outcomes from the time of initiation of dialysis for an average of 1.6 yr. Compared with nonuse, warfarin use associated with a significantly increased risk for new stroke (hazard ratio 1.93; 95% confidence interval 1.29 to 2.90); clopidogrel or aspirin use did not associate with increased risk for new stroke. Analysis using international normalized ratio (INR) suggested a dose-response relationship between the degree of anticoagulation and new stroke in patients on warfarin ($P = 0.02$ for trend). Warfarin users who received no INR monitoring in the first 90 d of dialysis had the highest risk for stroke compared with nonusers (hazard ratio 2.79; 95% confidence interval 1.65 to 4.70). Warfarin use did not associate with statistically significant increases in all-cause mortality or hospitalization. In conclusion, warfarin use among patients with both ESRD and atrial fibrillation associates with an increased risk for stroke. The risk is greatest in warfarin users who do not receive in-facility INR monitoring.

J Am Soc Nephrol 20: 2223–2233, 2009. doi: 10.1681/ASN.2009030319

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FMCNA

- 48825 patients
- 4.5% had atrial fib (2193)
- 1671 were included
  - 44.7% were on coumadin
  - 11.4% clopidogrel, 37.3% on ASA
  - 14.3 were on coumadin plus one other agent
  - 28.7% were on no OAC or APA

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Does warfarin decrease stroke risk?

Compared with nonuse, warfarin use associated with a significantly increased risk for new stroke (HR 1.93; CI 1.29 – 2.90)

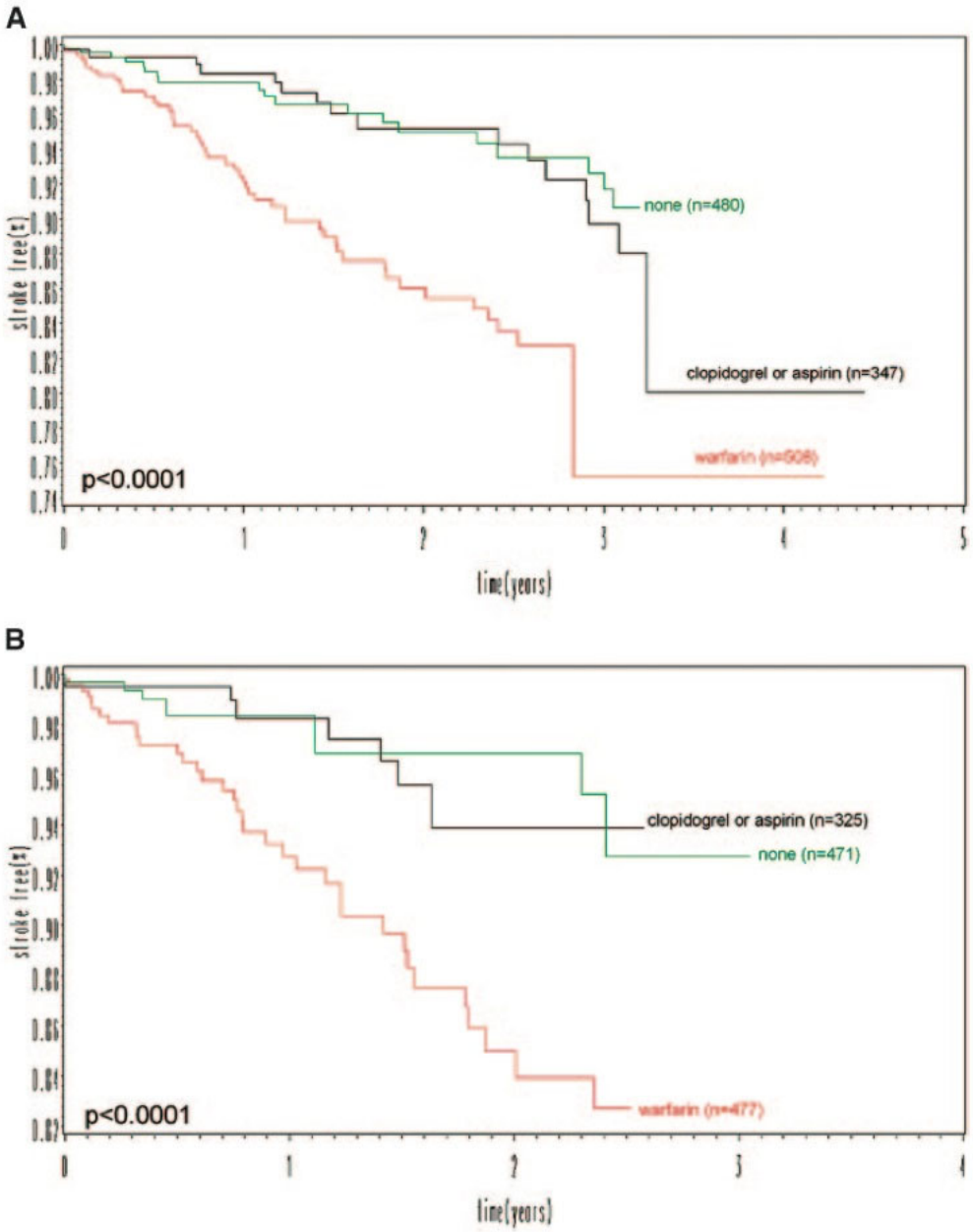


Figure 1. Crude stroke curves by drug exposure. (A) Under an intention-to-treat assumption, increased incidence of new stroke was associated with patients who were on warfarin. (B) Similar results were noted when patients were censored when they changed their warfarin, clopidogrel, or aspirin prescription after study enrollment.

	N	strokes (strokes per pt year) ischemic	hemorrhagic	$CHADS_2$
No INR monitoring available	204	23 (0.068)	6 (0.017)	2.7
INR>3	60	3 (0.031)	1 (0.011)	2.6
INR=2-3	272	19 (0.038)	6 (0.012)	2.8
INR=1.5-1.9	155	9 (0.029)	4 (0.013)	2.8
INR<1.5	56	3 (0.027)	0 (-)	2.7

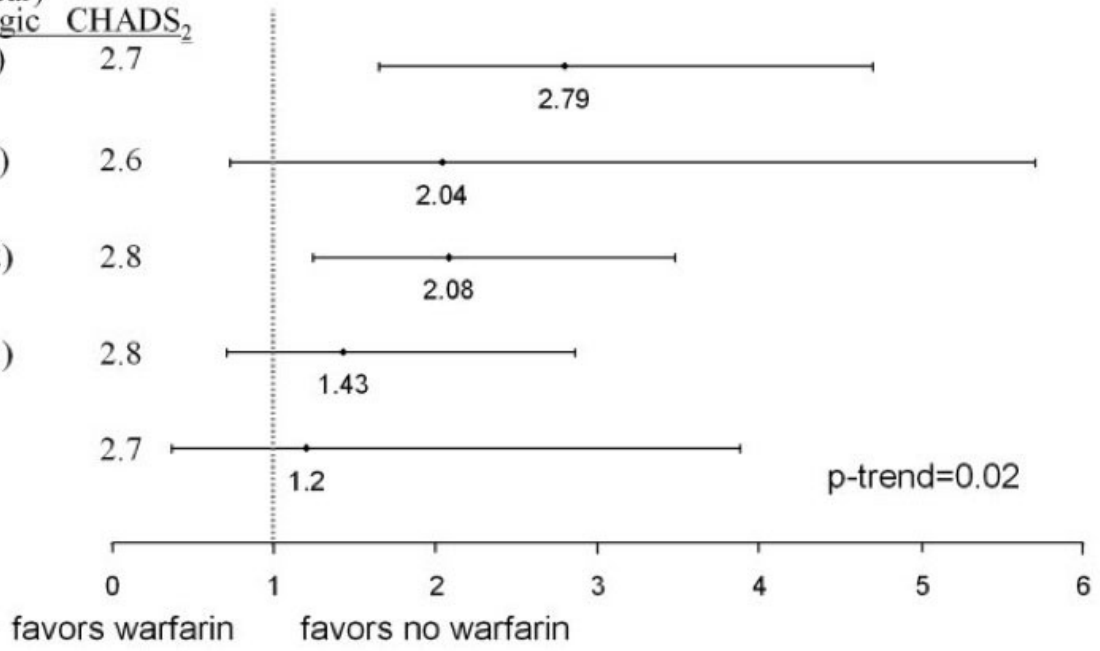


Figure 3. HRs for stroke with warfarin use (*versus* nonuse) by strata of INR level. The graph demonstrates a dose-response relationship between warfarin and new stroke. Patients with higher levels of anticoagulation, as quantified by the INR level, have an increased risk for new stroke ($P = 0.04$ for trend) with warfarin use (*versus* nonuse). Patients who were on warfarin and had no INR monitoring had the highest risk for new stroke. The stroke risk, as quantified by the $CHADS_2$ score, among the five categories of INR were statistically ($P = 0.11$) and clinically no different.

This suggests a dose response relationship between degree of anticoagulation and new stroke in patient on warfarin.

DOPPS

http://www.kidney-international.org

original article

Atrial fibrillation in hemodialysis patients: clinical features and associations with anticoagulant therapy

Volker Wizemann[1], Lin Tong[2], Sudtida Satayathum[2], Alex Disney[3], Takashi Akiba[4], Rachel B. Fissell[5], Peter G. Kerr[6], Eric W. Young[7,8] and Bruce M. Robinson[2,7]

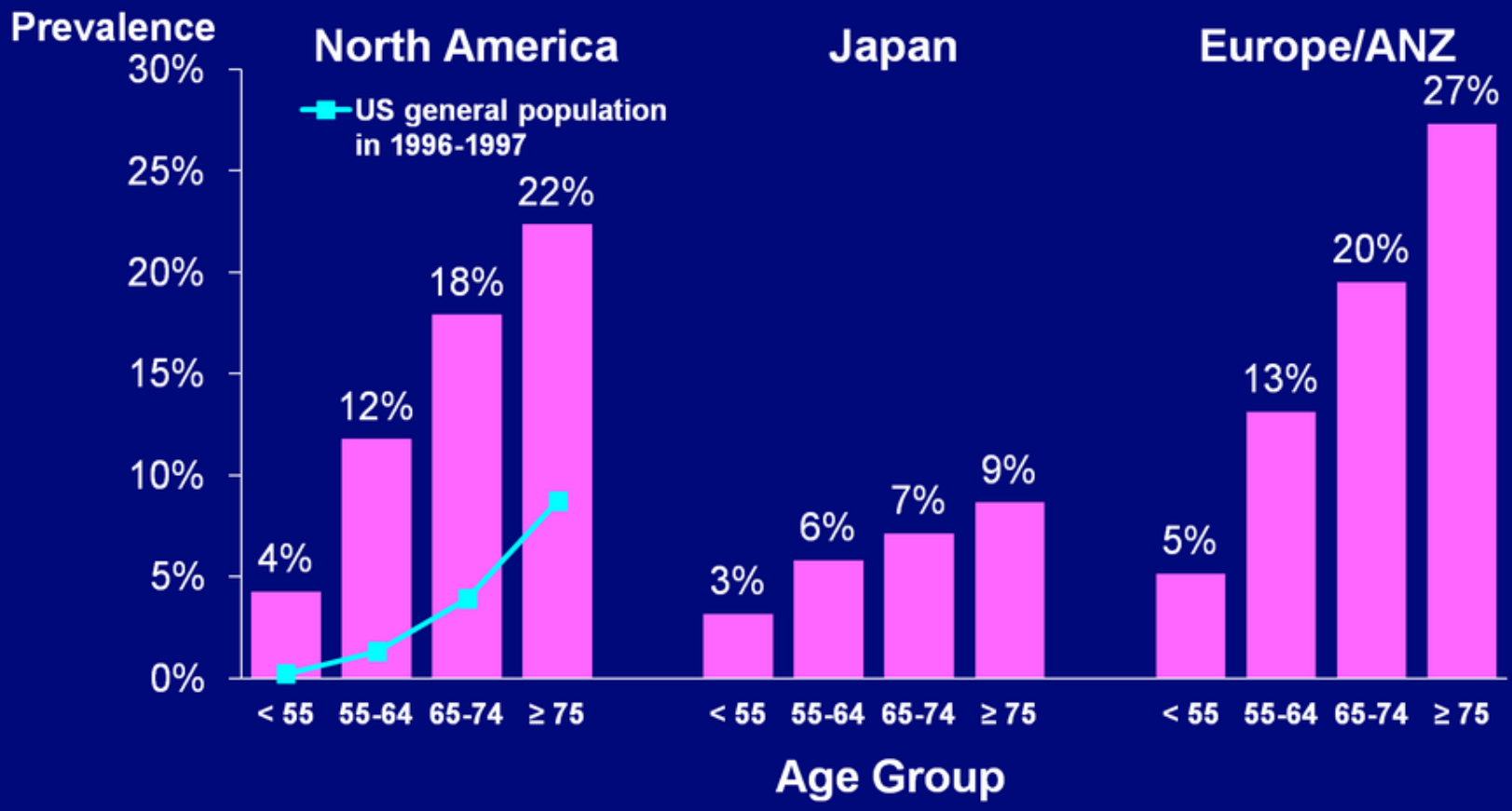
[1]Georg Haas Dialysezentrum, Giessen, Germany; [2]Arbor Research Collaborative for Health, Ann Arbor, Michigan, USA; [3]Renal Unit, Queen Elizabeth Hospital, Woodville, South Australia; [4]Tokyo Women's Medical University, Tokyo, Japan; [5]Cleveland Clinic, Cleveland, Ohio, USA; [6]Monash Medical Centre, Melbourne, Victoria, Australia; [7]University of Michigan, Ann Arbor, Michigan, USA and [8]Veterans Administration Medical Center, Ann Arbor, Michigan, USA

DOPPS

Atrial fib in DOPPS

- 17,513 randomly selected patients
- 2188 had AF (12.5%)
- Compared with patients without AF at enrollment, AF at enrollment was positively associated with all cause mortality and stroke (HR = 1.28, CI 1.01 – 1.62)

Figure 1: Prevalence of Diagnosed Atrial Fibrillation among HD Patients, Stratified by Region and Age

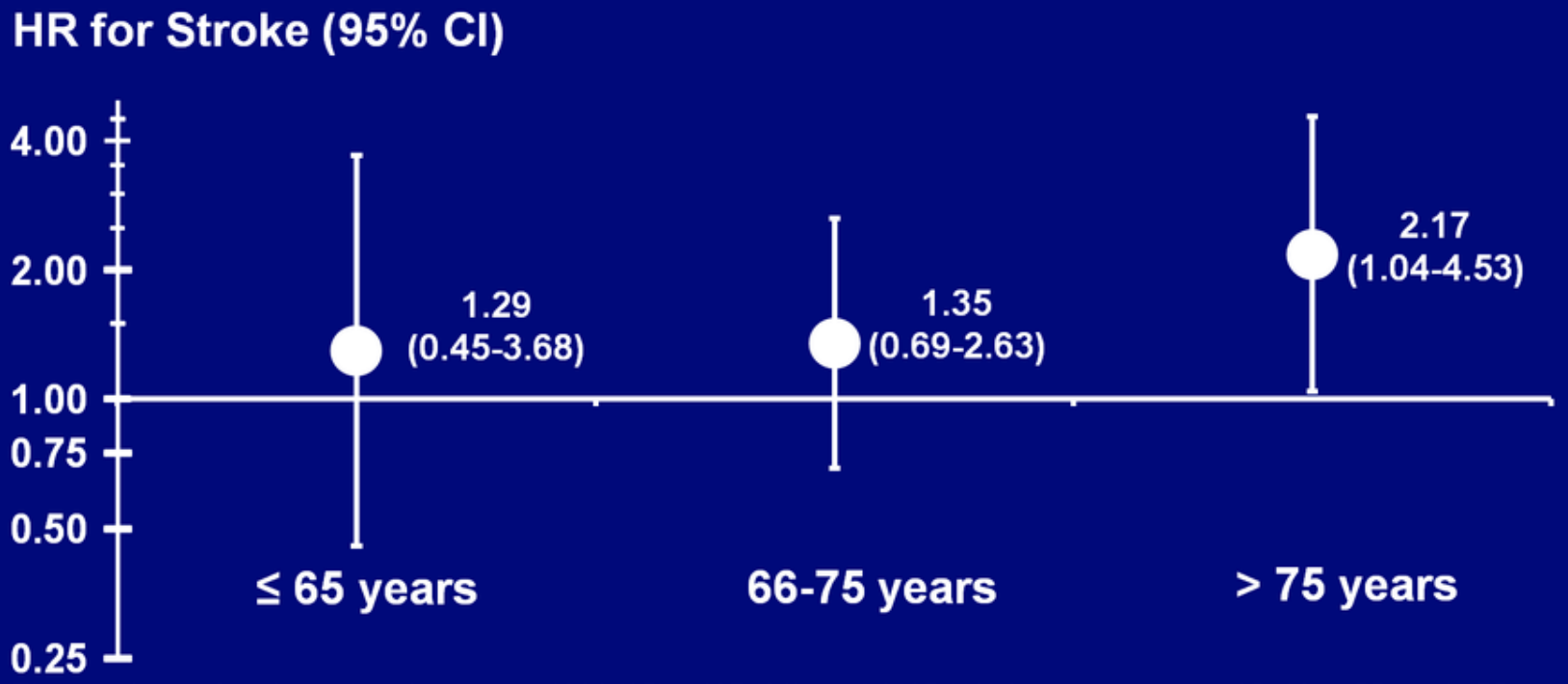


Prevalence of history of atrial fibrillation (AF) at DOPPS enrollment by region and age in prevalent cross-sections combining DOPPS I (1996-2001) and DOPPS II (2002-2004) (n=17,513). For comparison, the approximate prevalence of AF in the same age categories among 1.89 million adults in the US general population in 1996-1997 is also shown (ref.5).

DOPPS

V Wizemann et al. *Kidney Int.* 77:1098-1106, 2010

Figure 2: Relative Risk of Stroke According to Warfarin Use, by Age Categories, among Patients with a Pre-existing AF



The numbers of patients (strokes) were 1001 (35), 1137 (61), and 1107 (49) for age groups ≤ 65, 66 to 75, and >75 years, respectively. The numbers (%) of patients on warfarin were 146 (15%), 192 (17%), and 171 (15%) for age groups ≤ 65, 66 to 75, and ≤ 75 years, respectively. Patients with prosthetic heart valves (N=177) were excluded. Separate Cox models for each age category were used to estimate the hazard ratio and 95% confidence interval (whiskers) of first stroke after study entry, adjusted for age within the restricted category, sex, black race, years with ESRD, study phase, history of stroke, comorbid conditions as listed in Table 2, permanent pacemaker implanted, previous history of cardiac arrest, left ventricular hypertrophy, and valvular heart disease, stratified by region and study phase and accounting for effects of facility clustering. In addition to warfarin use, the following variables were statistically significant (P<0.05) in a model including all age categories: neurologic disease (P=0.02), diabetes (P=0.03), and previous history of stroke (P=0.002).

DOPPS

V Wizemann et al. *Kidney Int.* 77:1098-1106, 2010

Table 3. Medication Use Among Patients According to Atrial Fibrillation Status, by Region

	Medication (% Use)													
	Aspirin		Warfarin		Beta-Blocking Agents		Ca Channel Blocking Agents		ACE Inhibitors		Digoxin		Amiodarone	
Country/Region	AF	no AF	AF	no AF	AF	no AF	AF	no AF	AF	no AF	AF	no AF	AF	no AF
Belgium	33	31	7	3	31	30	2	2	19	23	3	2	25	3
France	27	20	5	1	18	21	9	6	20	20	11	1	46	6
Germany	37	31	2	2	34	34	12	8	37	30	4	0	7	1
Italy	24	21	14	5	7	9	7	5	13	16	24	6	29	2
Spain	25	17	4	0	11	13	9	4	15	14	25	2	22	2
Sweden	39	36	16	3	57	51	3	2	15	18	21	2	2	0
United Kingdom	46	35	24	11	31	23	2	4	21	24	21	2	22	1
EUR Overall	32	26	9	4	26	23	7	5	21	20	15	2	23	2
Australia-New Zealand	33	41	25	4	26	26	12	9	22	28	27	3	14	2
Canada	40	38	37	17	42	47	8	8	28	39	18	2	9	2
Japan	17	10	5	1	13	9	14	8	13	18	17	3	0	0
United States	30	25	26	8	31	30	17	9	22	24	33	8	8	1
Overall	31	23	16	5	27	23	11	7	21	22	22	4	15	1

Combined DOPPS I/II data (1996-2004); among baseline DOPPS I and II prevalent cross-sections (n=17,220). Patients with AF had "history of atrial fibrillation" at DOPPS enrollment.

DOPPS

V Wizemann et al. *Kidney Int.* 77:1098-1106, 2010

DOPPS: A fib in HD

- The risks and benefits of anticoagulation have to be carefully weighed on an individual basis. Additional studies (including RCT's) to evaluate the safety and efficacy of treatments for dialysis patients with A fib are indicated.

Coumadin use at HRRH (HD, N=~300)

- Coumadin for atrial fibrillation = 33
- Coumadin for line patency = 9
- Coumadin for other uses = 6
- Fragmin for line patency = 5
- No patients are on both fragmin and coumadin
- Patients with atrial fibrillation not on coumadin = 3 (we think)
  - DR (calcyphylaxis), PM (past GI bleed), MR (fall risk)

DOPPS

Conclusions re coumadin

- Based on all this observational data:
  - should there now be an RCT?
  - Does HRRH use too much coumadin for A fib and/or for CVC patency?
    - In the meantime, is this observational data enough to cause a change in practice?
- In a discipline like nephrology, what is the relative role of observational studies versus RCT's?
- How can we generate more and better evidence?

DOPPS

Conclusions about DOPPS

- DOPPS IV is ongoing
- New statistical methods make observational studies like DOPPS more similar to RCT's
- Well done observational studies can contribute a lot to a discipline like nephrology
- Further DOPPS expansion is limited only by funding (more countries, PD, CKD)
- DOPPS data can be examined locally to improve quality of care and outcomes
  - High Hb vs high ESA doses
  - Coumadin utilization

DOPPS


HA! THERE'S NO EVIDENCE I WAS LYING ON THEIR BEDS!
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