DETAILED METHODS

Study Design and Setting

We obtained data on patients receiving intensive and conventional hemodialysis from two multinational renal databases: the International Quotidian Dialysis Registry (IQDR), and the Dialysis Outcomes and Practice Patterns Study (DOPPS), respectively. To optimize baseline prognostic balance between groups, we matched patients by country, duration of ESRD before study enrollment (vintage), and propensity score. All analyses adhered to a detailed, pre-defined study protocol, and reporting was in accordance with the STROBE guidelines (Appendix A, below).[1]

Data Sources

Detailed methods for IQDR and DOPPS have been previously described.[2, 3] In brief, the IQDR captures detailed demographic, clinical, dialysis prescription, and outcomes data on incident and prevalent patients receiving more frequent (≥5 sessions/week) or long (>5.5 hours/session) hemodialysis. None of the patients received hemodialysis with the NxStage (NxStage Medical Inc., MA, USA) device. Participation in the IQDR is voluntary, and data are collected in 2 ways. Primary IQDR data were prospectively abstracted from medical charts and entered into web-based electronic case report forms by trained research personnel. Demographics and comorbidities were entered at the time patients were registered in the database. Prescription data, dialysis modality changes, transplantation and vital status were updated semi-annually. All centers confirmed vital status in August 2010. All patients provided written consent.

Secondary IQDR data were obtained through direct electronic transfer from the Renal Epidemiology and Information Network (REIN),[4] the Fresenius Medical Care North America (FMCNA), and the Patient Records and Outcome Management Information System (PROMIS) databases. REIN and

PROMIS prospectively capture detailed data for all patients receiving dialysis in France and British Columbia, Canada, respectively, while FMCNA does the same for patients receiving hemodialysis in facilities run by Fresenius in the United States. Comorbidities were entered when patients began renal replacement therapy, while prescription, vital status and modality changes were updated as they occurred. De-identified extracts on patients receiving frequent or long hemodialysis in these databases were prepared according to variable coding used by the IQDR.

The DOPPS prospectively captures detailed patient- and facility-level data on randomly selected subjects from randomly selected hemodialysis units in 13 participating countries.[2] All patients provided written consent. Trained research personnel abstracted demographic, clinical, and dialysis prescription data from medical charts at the time of patient entry into DOPPS. Vital status, transplantation, and dialysis modality switches were updated every 4 months.

Data collection periods were: January 1st 2000 - August 4th 2010 (primary IQDR data), January 1st 2002 - December 31st 2008 (REIN), June 1st 2002-August 14th 2010 (PROMIS), January 1st 2007 – March 4th 2009 (FMCNA), and January 1st 2002 - December 31st 2008 (DOPPS).

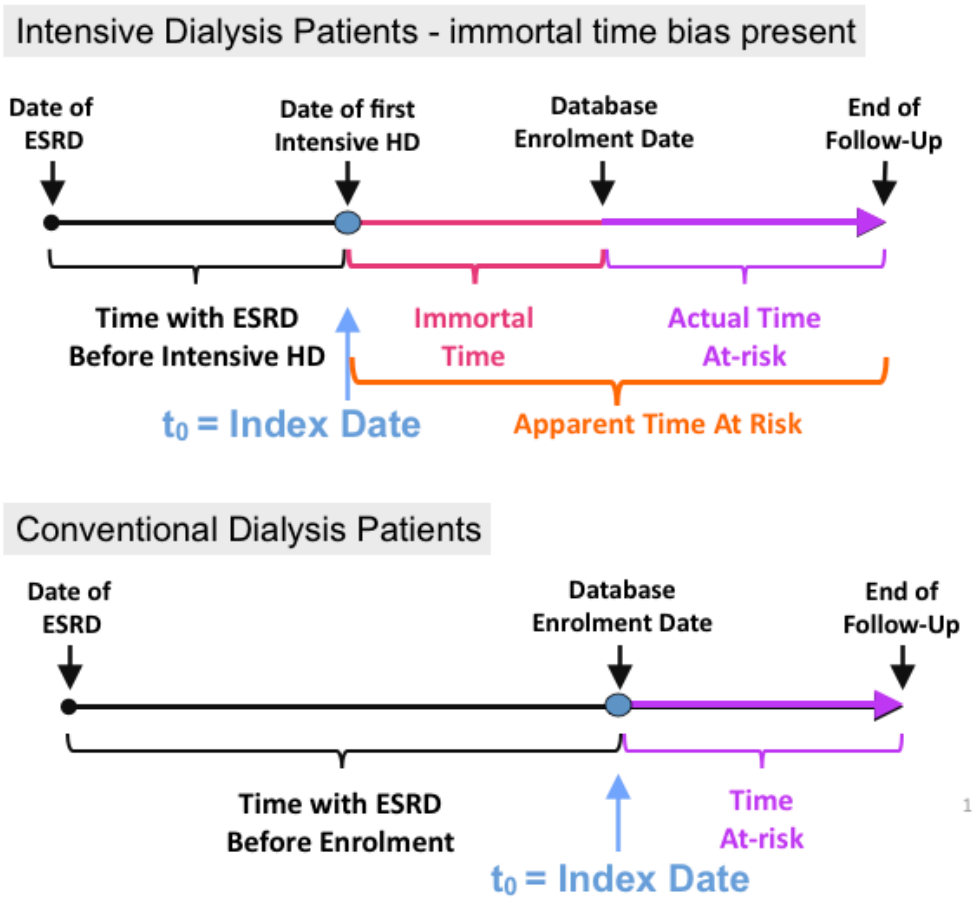
Study Sample

All participants were ≥18 years old at enrollment. We included patients receiving intensive hemodialysis, defined as ≥5.5 hours/session (day or overnight), 3-7 sessions/week. Intensive hemodialysis was performed at home. For the comparator group, we selected patients receiving conventional hemodialysis for < 5.5 hours/session, 3 sessions/week, in a clinic or hospital setting.

Time Interval Computation and Elimination of Immortal Time Bias

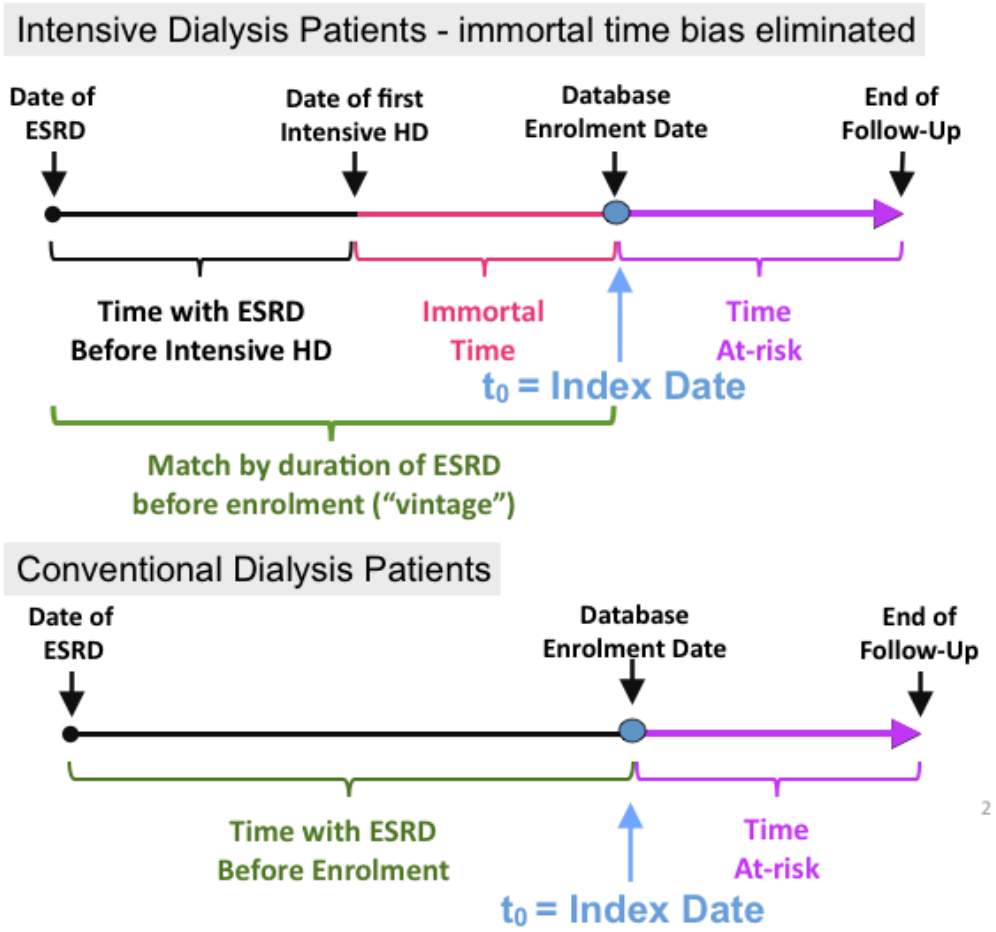
The study cohort included a combination of incident (consecutive) patients or "new users", and prevalent patients who were started on intensive hemodialysis prior to study database enrolment. In the event that incident patients were included, there was no risk of immortal time bias.[5] However, prevalent patients who had accrued follow-up time on intensive hemodialysis prior to study enrollment, may have theoretically introduced immortal time bias into survival time computations. The time interval between date of first intensive hemodialysis and enrolment represents an "immortal" window, during which patient death is not possible. This would result in an overestimate of relative survival time.

Figure 1. Introduction of immortal time bias by sampling prevalent hemodialysis patients.



In order to prevent immortal time bias (Figure 2), we used the enrollment date as the index date in both exposure groups.

Figure 2. Elimination of immortal time bias by using the database enrolment date as index date.



As a result, we obtained more conservative estimates of "vintage" (time with ESRD prior to enrollment) and time at-risk (survival). More specifically, patients receiving independent dialysis were matched to patients on conventional hemodialysis who were alive for at least as long prior to the study follow-up (time at-risk).

Coding for Comorbid Conditions

Comorbidities coded with the ICD-9 classification (FMCNA data) were re-classified into Charlson Comorbidity Index definitions for standardization purposes, but were treated as individual covariates in statistical models.[6]

Matching Procedures

We selected patients from the above-defined cohorts using propensity-score matching to account for systematic differences between conventional and intensive hemodialysis patients. The propensity score is the probability of receiving intensive hemodialysis, conditional on the observed baseline covariates.[7] Conventional and intensive hemodialysis patients with the same propensity score will have similar distributions of observed baseline covariates, reducing the impact of selection bias.

We estimated propensity scores with logistic regression, regressing type of hemodialysis (intensive vs. conventional) using the following covariates: age, sex, diabetes, myocardial infarction, congestive heart failure, cerebrovascular disease, cancer, race, and dry weight.[8] Variables were chosen for the propensity score model based on their associations with mortality or treatment selection.[8] Laboratory and blood pressure variables were not included in the propensity-score models as they were obtained after patients started intensive hemodialysis. We estimated the propensity score model separately for each country. We excluded patients receiving conventional hemodialysis with a propensity score <0.001, so that patients on conventional hemodialysis had a non-zero probability of receiving intensive hemodialysis. The distribution of propensity scores between groups is shown in Appendix B (see below).

We then matched patients by country, duration of ESRD (±6 months), and propensity score, with up to 10 conventional hemodialysis patients for each intensive hemodialysis patient, using a "greedy-matching" (nearest-neighbor) algorithm.[7] We compared differences between matched conventional and intensive hemodialysis patients using standardized differences.[9] We evaluated various caliper widths iteratively until between-group standardized differences were minimized. The final selected propensity score caliper width was 0.06. Each conventional patient variable was weighted by the inverse of the number of conventional patients in that matched set when computing standardized differences.

Primary Survival Analysis

The primary outcome was all-cause mortality. For the primary analysis, we attributed all deaths to dialysis modality at index date, regardless of switches to other dialysis modalities. Patients were censored at transplantation in all analyses, as transplantation was considered a favourable outcome. We used the Kaplan-Meier product-limit method to calculate cumulative death rates and construct survival graphs for each group, and used the two-sided stratified log-rank test to compare differences between the curves.[10] We used Cox regression with and without multivariable adjustment to model survival. Models were stratified on the matched sets. The adjusted model included covariates in Table 1 that had standardized differences of >10 percent.[11] We excluded laboratory values and blood pressure from the multivariable models as they are influenced by intensive hemodialysis and were only available after the start of intensive hemodialysis. To test the proportional hazards assumption, we performed a global test of time-dependent covariates which were created for all covariates in the model.[12] In models where the proportional-hazards assumption was not valid, we introduced time-dependent covariates to allow these covariates to have a time-varying effect. We used linear regression to compare lab and blood pressure measurements between groups. We calculated 95% confidence intervals for all hazard ratios, and

interpreted a two-tailed p-value < 0.05 as statistically significant. Missing data were not imputed. We used SAS 9.2 (SAS Institute Inc., North Carolina, USA) for all analyses.

Sensitivity Analyses

We repeated the primary survival analysis with a range of alternative scenarios and methods as follows:

1. We repeated the primary analysis with censoring of outcomes 90 days after a permanent modality switch; deaths within 90 days of a switch were attributed to the dialysis modality at index date.
2. Many-to-one matching can theoretically introduce selection bias and inflate treatment effect estimates.[13] We therefore repeated the primary analysis with 2:1 matching.
3. In order to isolate the effect of dialysis duration (and eliminate the effect of treatment frequency), we restricted the analysis to matched sets in which intensive hemodialysis patients received 3 treatments per week.
4. Since the inclusion of prevalent patients may have theoretically introduced survivor bias (we did match by vintage to eliminate survivor bias), we separately analyzed matched sets in which intensive hemodialysis patients were newly started on intensive hemodialysis ("new users") at the time of cohort entry.
5. In order to assess the potential impact of information bias arising from multiple secondary data sources, we repeated the primary analysis with subjects from each secondary data source (FMCNA, REIN, and PROMIS) excluded.
6. In order to evaluate the significance of missing vascular access data, we conducted a 'worst case scenario' sensitivity analysis in which we repeated the primary survival comparison with the assumption that all patients with missing access type at baseline had fistulae in the intensive hemodialysis group, and catheters in the conventional hemodialysis group.

7. To examine for potential era effects, we repeated the primary analysis but this time also matched on year of index date.
8. Finally, we constructed a multivariable Cox model that included *all* eligible patients (without matching). This model was stratified by country, and included covariates achieving $p<0.1$ using the method of two-variable screening.

Subgroup Analyses

We repeated the primary analysis in 5 pre-defined subgroups: age, country, cardiovascular disease (a composite of myocardial infarction or congestive heart failure), duration of ESRD before index date, and dialysis frequency (3-4 vs. ≥ 5 sessions per week). We used median values in the intensive hemodialysis group as the cut-point for continuous variables. For each subgroup, we re-matched patients based on the subgroup cut-off, while matching on propensity score, vintage, and country as in the primary analysis. We performed statistical tests for interaction to determine if the hazard ratios for intensive hemodialysis and mortality differed significantly among subgroups.[14] To do so we conducted a series of pair-wise comparisons using standard z-tests.[15]

APPENDIX A: STROBE[16] Statement checklist.

	Item No	Recommendation	Location in Report
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	**Title and Abstract**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	**Abstract**
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	**Introduction, para. 1-2**
Objectives	3	State specific objectives, including any pre-specified hypotheses	**Introduction, para. 2**
Methods			
Study design	4	Present key elements of study design early in the paper	**Methods, para. 1**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	**Methods, para. 1**
Participants	6	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	**Methods, para. 2-6**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	**Methods, para. 7**
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	**Methods, para. 2-5**
Bias	9	Describe any efforts to address potential sources of bias	**Methods, para. 8-10**
Study size	10	Explain how the study size was arrived at	**N/A**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	**Methods, para. 7**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	**Methods, para. 8-10**
		(*b*) Describe any methods used to examine subgroups and interactions	**Methods, para. 13**
		(*c*) Explain how missing data were addressed	**Figure 1**
		(*d*) If applicable, explain how loss to follow-up was addressed	**N/A**
		(*e*) Describe any sensitivity analyses	**Methods, para. 12**
Results			
Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed	**Results, para. 1-2**
		(b) Give reasons for non-participation at each stage	**Figure 1; Results, para. 3**
		(c) Consider use of a flow diagram	**Figure 1**
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	**Table 1**
		(b) Indicate number of participants with missing data for each variable of interest	**Figure 1**
		(c) Summarize follow-up time (eg, average and total amount)	**Results, para. 3**

Outcome data	15	Report numbers of outcome events or summary measures over time	**Results, para. 3**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	**Results, para. 3-4**
		(*b*) Report category boundaries when continuous variables were categorized	**N/A**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	**Results, para. 5**
Discussion			
Key results	18	Summarize key results with reference to study objectives	**Discussion, para. 1**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	**Discussion, para. 5**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	**Discussion para. 6**
Generalizability	21	Discuss the generalizability (external validity) of the study results	**Discussion para. 3**
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	**Page 1**

APPENDIX B: PROPENSITY SCORE MODEL AND HISTOGRAMS

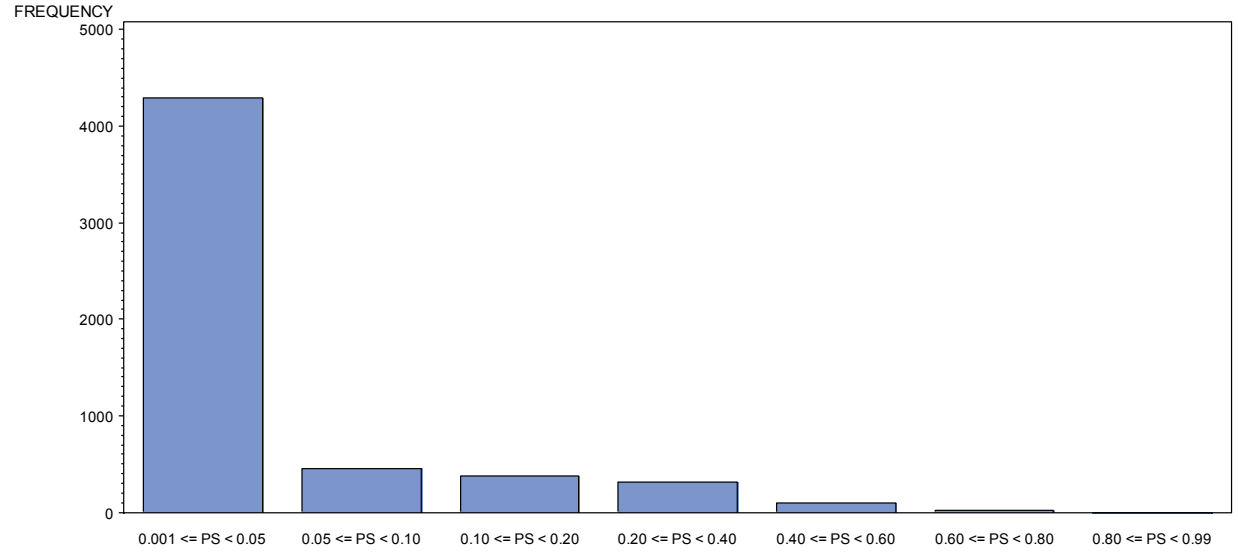
Final propensity score estimation model:

```
proc logistic data=anal13_CA descending outest=psest covout;
      model treatment = age_at_index gender dry_wt DM MI CHF POVD CVD
                        / lackfit ;
      output out=pspred_CA pred=psprob ;
run;
```

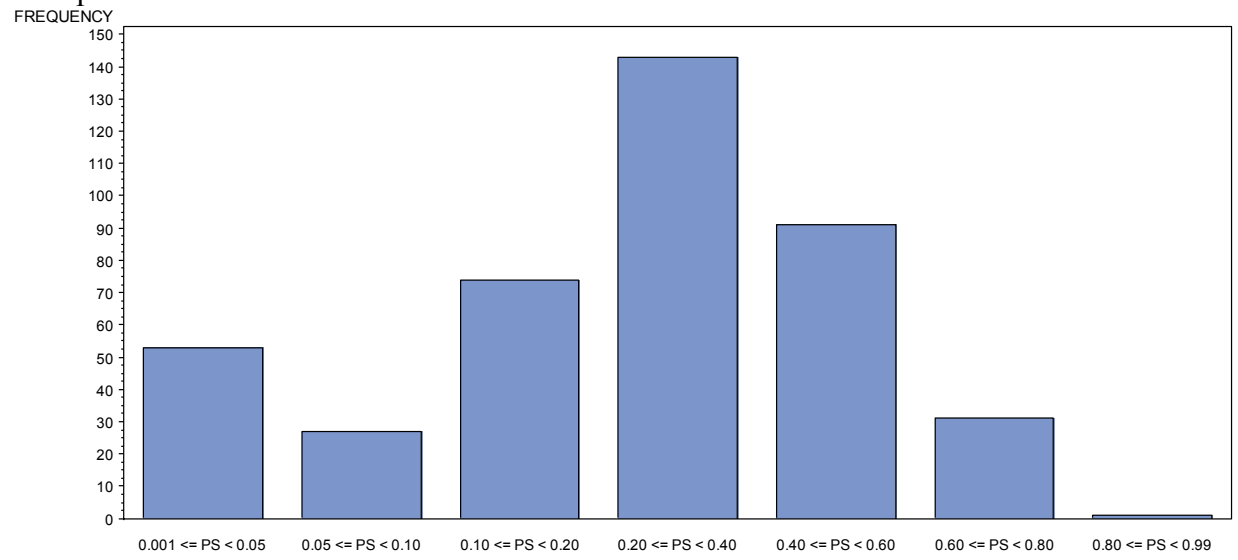
(repeat for US and FR)

Histograms of propensity scores - overall:

CHD patients:

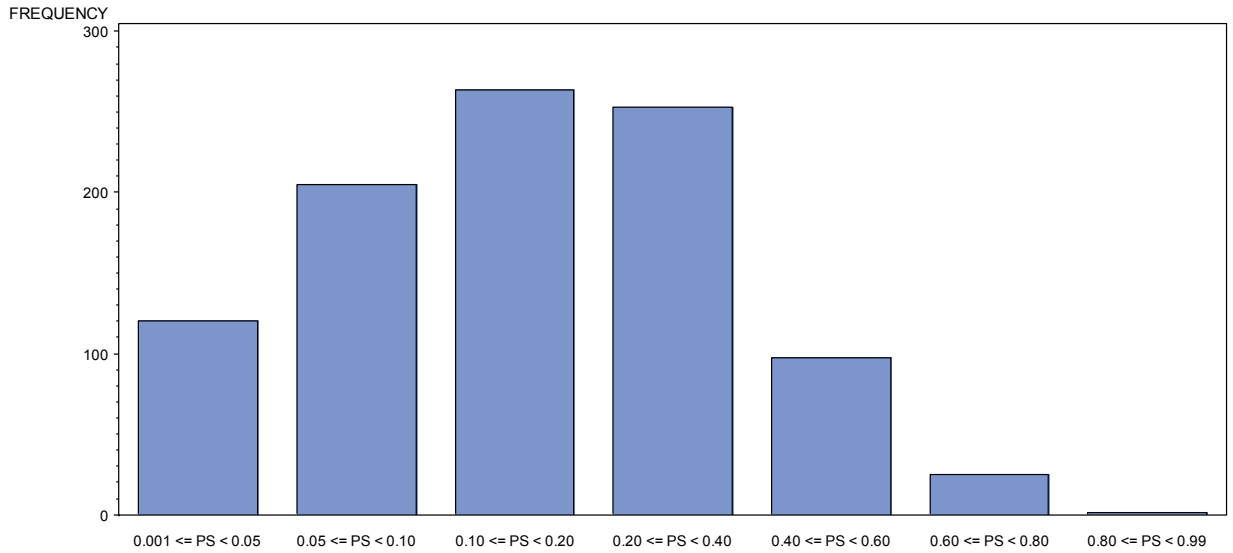


LHD patients:

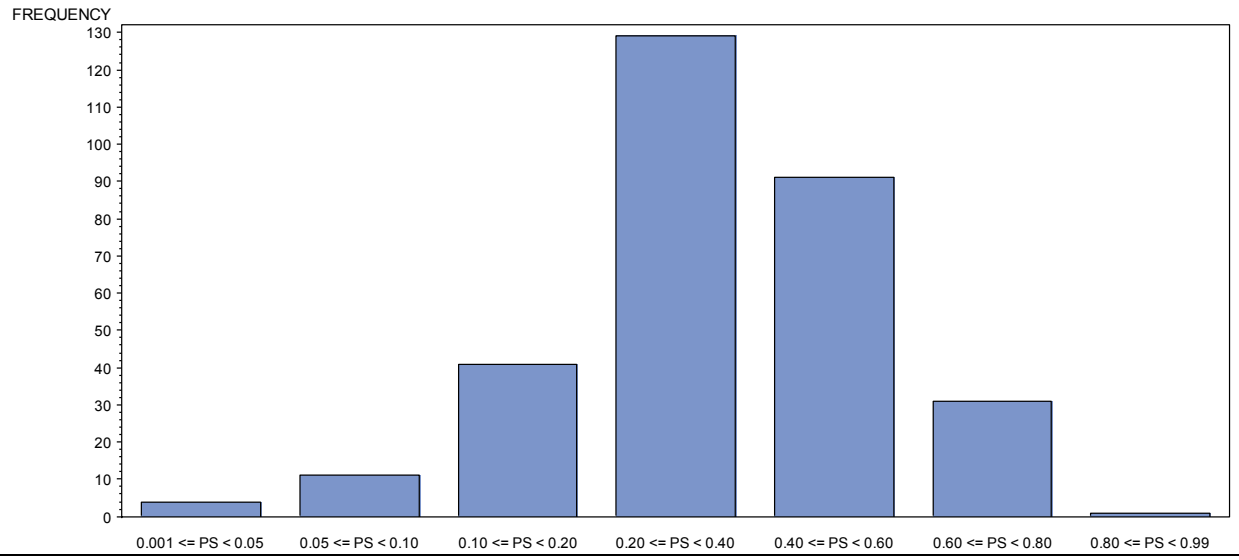


Histograms by country:

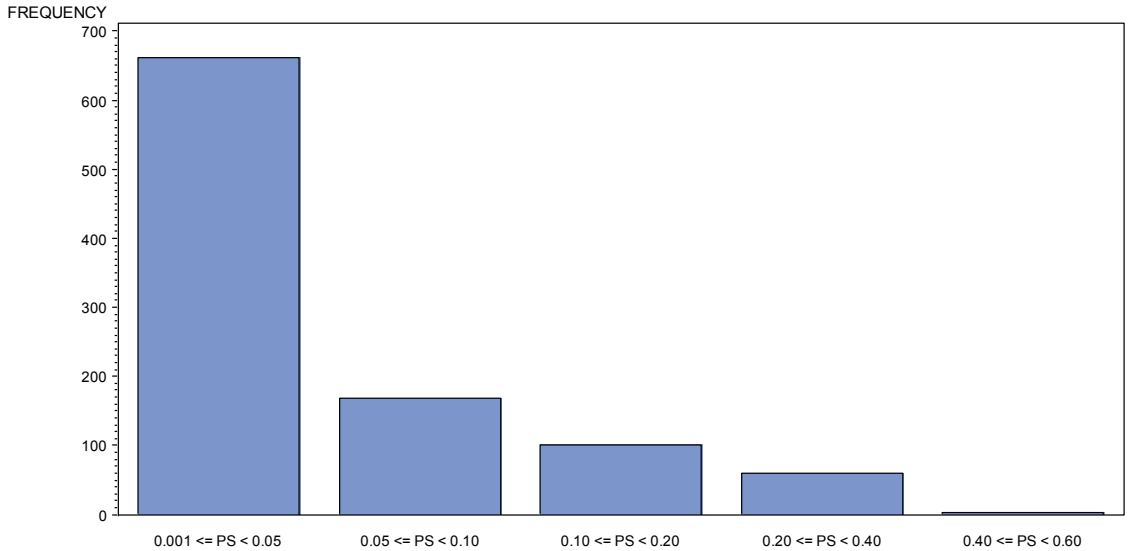
Canada - CHD



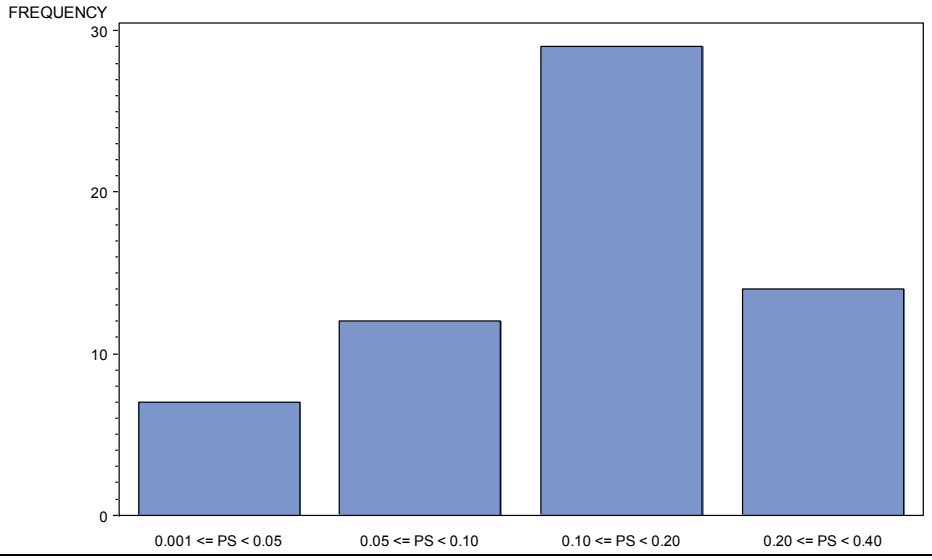
Canada – LHD



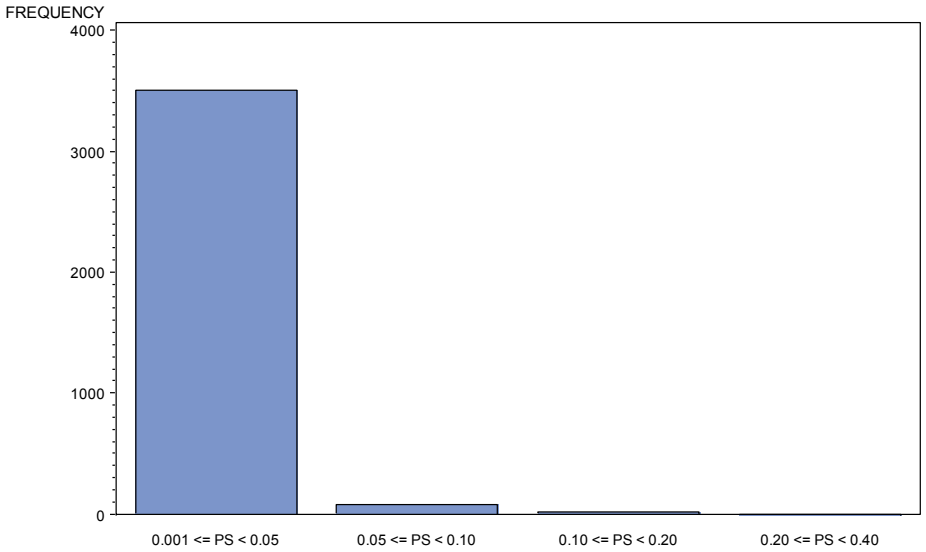
France – CHD



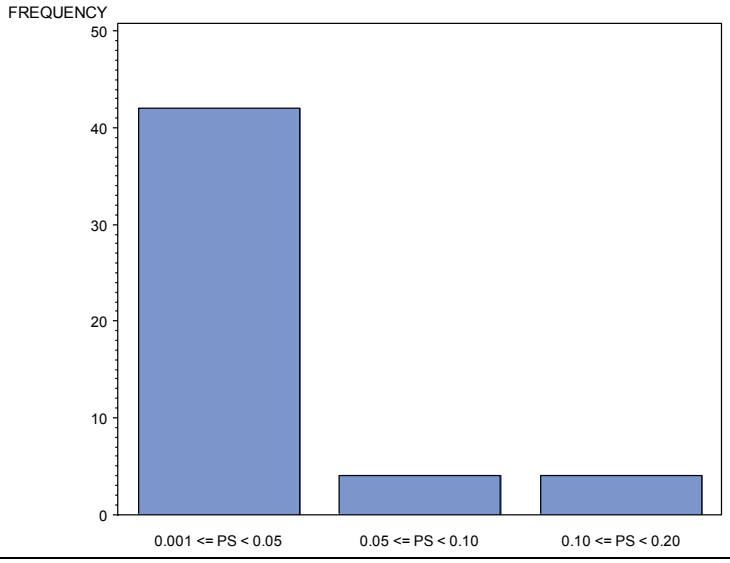
France – LHD



US – CHD


FREQUENCY
4000
3000
2000
1000
0
0.001 <= PS < 0.05
0.05 <= PS < 0.10
0.10 <= PS < 0.20
0.20 <= PS < 0.40

US – LHD


FREQUENCY
50
40
30
20
10
0
0.001 <= PS < 0.05
0.05 <= PS < 0.10
0.10 <= PS < 0.20

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