Personalized Medicine and Patient Selection: Discretion vs. Guidelines

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Big picture: Personalized guidelines

- Lots of interest in "personalized medicine" using "big data"
  - Use each patient's entire medical history to predict treatment effects
- Abaluck and Agha (2016) suggests first-order mistakes in doctor decisions
  - CT scan ordered for wrong patients 5x more important than overuse of testing
- How can we develop personalized guidelines in settings with patient selection?

Goals of this project

1. Do doctors respond to existing guidelines?
2. Would doctors do better with strict adherence to existing guidelines?
3. How much better would optimal (strict) guidelines do?
4. (not today) Compare strict guidelines to discretionary guidelines

Our context: Prescriptions to prevent stroke

- Warfarin is used to prevent stroke among patients diagnosed with atrial fibrillation
- Warfarin also increases bleed risk
- CHADS2 score predicts stroke risk
  - based on history of congestive heart failure, hypertension, age, diabetes and stroke
- Yet 40-50% of patients considered high risk by guidelines are not given warfarin (Glazer et al. 2007)

Are doctors minimizing rate of strokes for a given number of bleeds?

Shortcomings of medical approaches to guideline development

- Doctors use risk among untreated patients to formulate treatment guidelines. This doesn't take into account:
  - Treatment effects need not be proportional to risk
  - Many combinations of x's to choose from (and nonlinearity)
  - Selection:
    - Relationship between x and risk among untreated patients biased if x impacts treatment decisions
    - Treatment effects may vary with treatment propensity

Shortcomings of current ML approaches to guideline development

- Computer science and operations research have begun to apply machine learning to suggest guidelines
  - Allows consideration of rich set of patient characteristics (and interactions)
  - Typically fail to account for selection

Innovations for guideline development

- Jackknife instrumental variable based on quasi-random assignment of patients to physicians
  - Aizer and Doyle 2013; Kling 2006
- Machine learning for variable selection
  - Apply LASSO following Belloni, Chernozhukov and Hansen 2014 + a generation of computer scientists
- Explicit modeling of heterogeneous treatment effects given selection on unobservables
  - Heckman and Vytlacil 2004

General applications of our econometric framework

How should decision-makers select people to treat in order to maximize known objective?

- Employer deciding which applicants to hire to maximize productivity
- Bank deciding which consumers to loan to at a given interest rate to minimize defaults
- Colleges deciding which applicants to admit (if we know objective at least…)

Outline for today

- Data
- Reduced form impact of existing guidelines on treatment decisions
- Model of patient bleed & stroke outcomes
- Identification & estimation approach
- Predicted treatment effects by risk quantile
- Simulated outcomes under differing decision regimes

Data

Electronic health records from the Veterans Health Administration

- 400,000 atrial fibrillation patients
- treated by 40,000 primary care physicians
- 13 years of data

Observe pretty much everything (that is recorded!) about these patients…

Variables to predict treatment effects

Categories	Variables
Demographics	Age, gender, ethnicity
CHADS2 Score	Age >= 75, hypertension, diabetes, congestive heart failure, stroke
Elixhauser	AIDS, alcoholism, anemia, arthritis…
Relevant medical history variables	Stroke family history, bleed personal history & family history, fall risk, vision problems, etc…
Lab values	Hemoglobin, hematocrit, platelets, albumin (coming soon)

Data

Cohort: patients with new diagnosis of atrial fibrillation and visit to PCP

Treatment variable: prescribed warfarin within 3 months of diagnosis

Outcome variable: stroke or bleed within 6 months

- Inpatient diagnosis at VA hospitals
- Fee basis data for strokes or bleed outside VA system reimbursed by VA
- Medicare claims data to capture care outside VA

Table 1: CHADS2 Score Guidelines

CHADS2 Stroke Risk Score	
Congestive heart failure history	+1
Hypertension history	+1
Age ≥ 75 years	+1
Diabetes mellitus history	+1
Stroke or TIA symptoms previously	+2

Clinical recommendations

Score of 2 or greater: high risk of stroke, oral anticoagulation recommended

Score of 1: moderate risk of stroke, oral anticoagulation considered

Score of 0: low risk of stroke, no anticoagulation recommended

Bleed and Stroke Rate by CHADS2 score

CHADS2	Observed Stroke Risk	Observed Bleed Risk	Warfarin Rate
0	0.016	0.025	0.474
1	0.021	0.030	0.520
2	0.029	0.040	0.549
3	0.050	0.053	0.552
4	0.113	0.060	0.544
5	0.152	0.071	0.549
6	0.166	0.095	0.487

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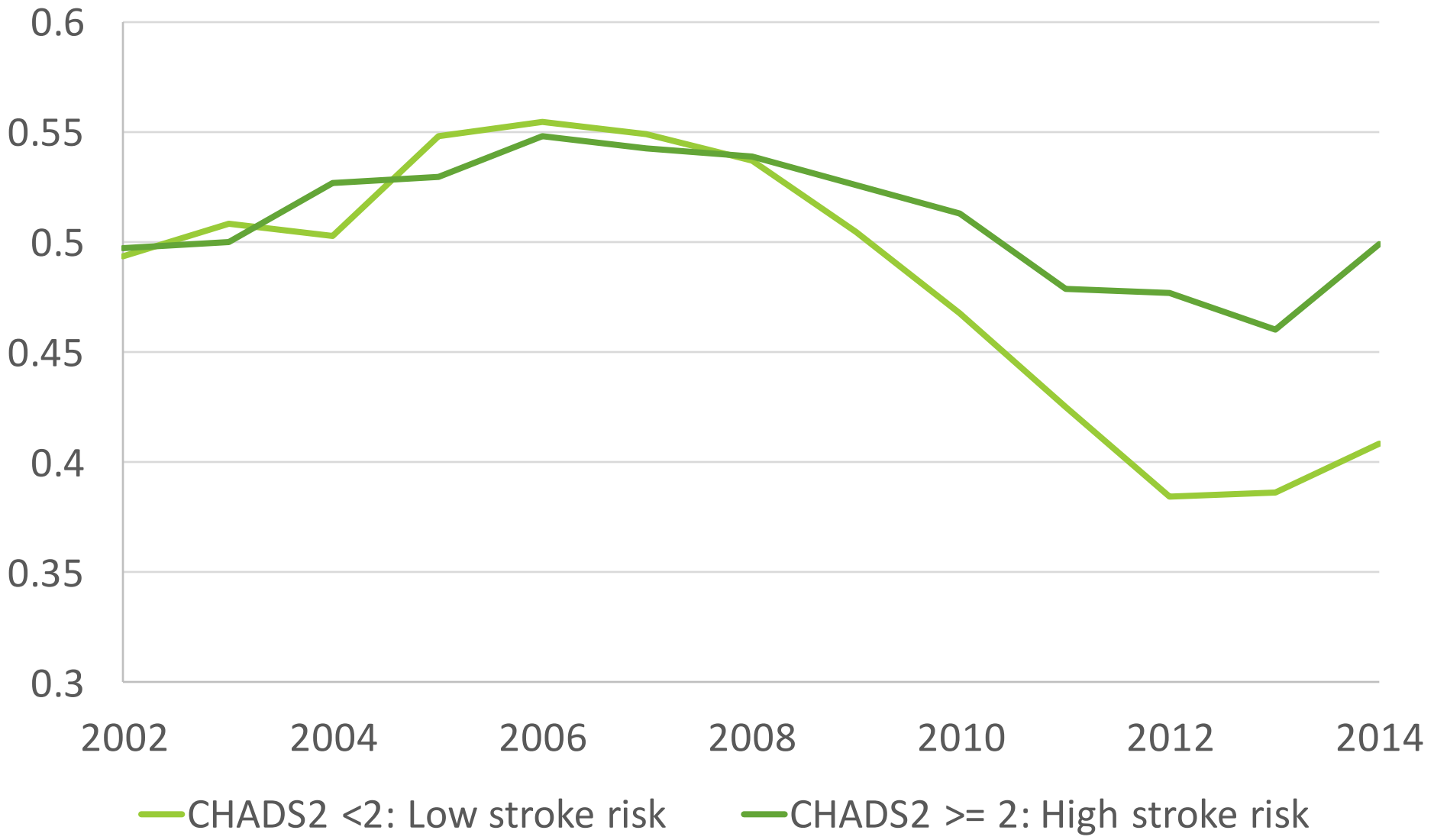
Measuring CHADS2 Score Use

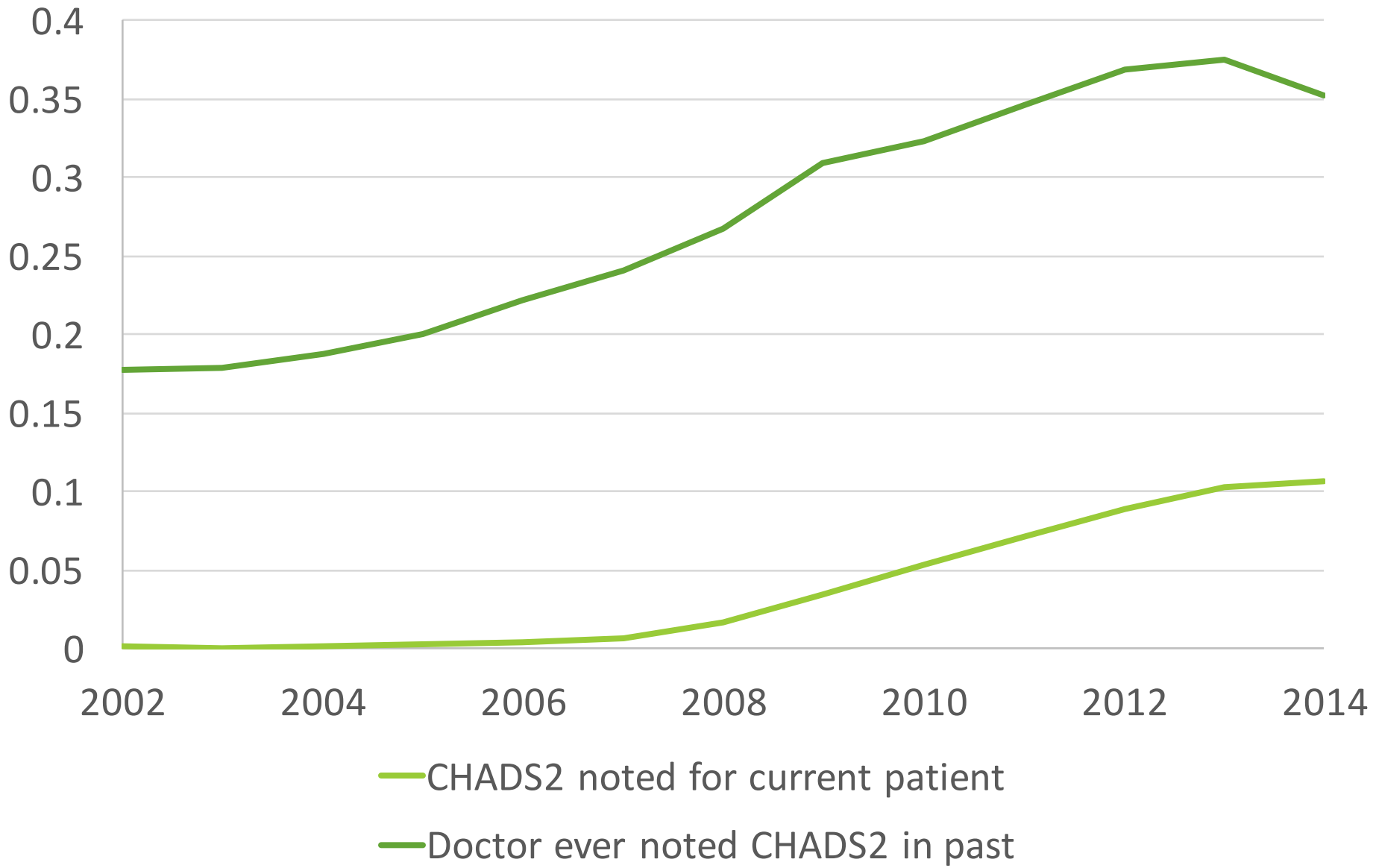
Two approaches:

1. We can reconstruct the CHADS2 score and observe physician behavior changes at different CHADS2 scores
2. We observe whether a doctor notes that they used the CHADS2 score (but doctor might not always write it down)

Trends in Warfarin Prescription Rates



Diffusion of CHADS2 Score over Time



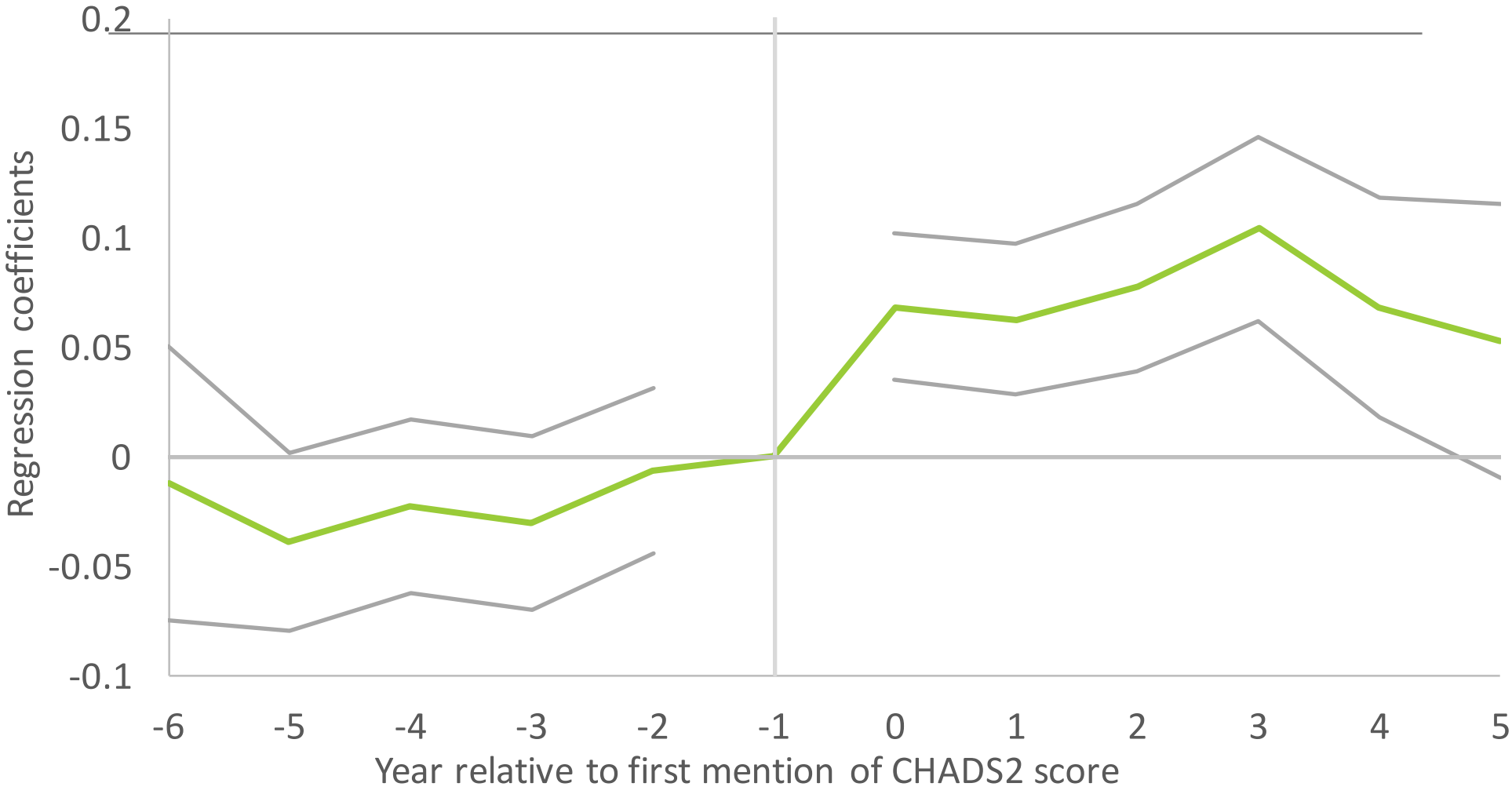
Diff-in-diff estimation of CHADS2 adoption on warfarin use

- Restricting the sample to doctors who mention CHADS2 at least once
- Does warfarin use amongst high CHADS score patients increases relative to low CHADs score patients after first CHADS2 mention?
- r indexes year relative to first mention of CHADS2

$$Warfarin_{idtr} = \sum_{r} \beta_r AdoptionYear_r(CHADS2_i \geq 2) + \alpha_t + \delta_r + \gamma_d + x_{id}\gamma + \epsilon_{idtr}$$

- Include doctor, time, CHADS2 score (and other covariates), and relative year fixed effects

Change in relative prescription rates for high score vs. low score patients after doctor's first CHADS2 mention



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Modeling patient outcomes

Y is stroke or bleed outcome variable:

Potential outcome without warfarin

Potential outcome with warfarin

$$Y_{id}(W = 0) = f(x) + \eta_{0id}$$
$$Y_{id}(W = 1) = h(x) + \eta_{1id}$$

- x's include patient, doctor and clinic characteristics
- $E(\eta_{0id}|x) = E(\eta_{1id}|x) = 0$ (by definition)

Doctors treat if:

$$B_{id} = g^*(x) + \eta'_{id} > 0$$

- Doctor's decision doesn't have to be rational

Modeling the ATE and LATE

$$E(Y|x, W = 1) = h(x) + \lambda_x^+(P(W|x))$$

$$E(Y|x, W = 0) = f(x) + \lambda_x^-(P(W|x))$$

$$\lambda_x^+(1) = \lambda_x^-(0) = 0$$
$$ATE = h(x) - f(x)$$
$$MTE = h(x) - f(x) + \Delta\lambda_x(P(W|x))$$

Restrictions on selection correction

$$E(Y|x, W = 1) = h(x) + \lambda_x^+(P(W|x))$$

$$E(Y|x, W = 0) = f(x) + \lambda_x^-(P(W|x))$$

$$\lambda_x^+(1) = \lambda_x^-(0) = 0$$

We will make assumptions so that:

$$\lambda_x^+ = \lambda_{A(x)}^+$$
$$\lambda_x^- = \lambda_{A(x)}^-$$

In baseline estimation, *A(x)* are decile of stroke risk conditional on *x*

Restrictions on selection correction

$$Y_{id}(0) = f(x) + \eta_{0id}$$
$$Y_{id}(1) = h(x) + \eta_{1id}$$

Doctors treat if:

$$B_{id} = g^*(x, \theta_d) + \eta'_{id} > 0$$

Sufficient for $\lambda_x^+ = \lambda_{A(x)}^+$ and $\lambda_x^- = \lambda_{A(x)}^-$ is:

distribution of $\{\eta_{0id}, \eta_{1id}, \eta'_{id}\}$ does not vary with x_{id}

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Identification

- Imagine you see lower stroke rate among treated than untreated patients for a given set of x's
  - This could be a direct estimate of the treatment effect
  - Or, could underestimate size of treatment effect if treated patients would have had even more strokes absent treatment
- We use quasi-random variation in proportion treated to identify treatment effects
- Single-index assumption to extrapolate treatment effect to other patients

Instrumental variable: Jackknife treatment propensity

- Assuming literal random assignment can construct instruments using the "leave-one-out" propensity to treat for each doctor (Aizer and Doyle 2014)

$$Z_{id} = \frac{1}{N_d - 1} \sum_{j \neq i} W_{jd}$$

- Doc A treats 30/100, doc B treats 20/100 – estimate impact of treatment for marginal patients
- In the VHA, patients are quasi-randomly assigned to doctors within a clinical site for primary care

Empirical Bayes adjustment to instrumental variable

- IV is much more precise for doctors who treat a larger number of in sample patients
- Basic jackknife also doesn't account for drift in prescription behavior over time
  - We derive an "empirical Bayes" estimator to do both (similar to Chetty, Friedman and Rockoff 2014)
  - Weighted average of results in each (doc, time), with doctor-specific weights, jackknife in current period ($nR^2 \sim 889$)

IV Estimates

Three concerns:

1. Do we really have quasi-random assignment?
   - Check covariate balance
2. Docs who treat more do other stuff differently?
   - Control for other differences in treatment
3. Monotonicity violations
   - Compare sign of first stage for each subset of patients
   - Are docs who treat more are better at figuring out which patients to treat? Can assess in structural model

Balance Test (t-stats) by quintile of instrumental variable

Clinic fixed effects partialled out

	Female	Age	Hispanic	Past Stroke	Past Bleed	Hypertension	Diabetes	CHF
q2	0.69	0.13	1.15	1.46	0.21	0.28	-0.35	0.13
q3	0.52	0.11	-0.45	0.16	2.03	0.94	-0.24	1.16
q4	0.51	0.64	0.38	-0.66	-0.74	2.13	0.72	-0.44
q5	-0.94	-0.24	-0.15	0.02	0.87	1.29	-0.75	0.73

Estimation: simplest version

Regression warfarin on covariates, clinic fixed effects and IV, generate $P(W|x)$:

$$P(W|x) = x_{id}\beta + IV_{d(-i)} + \theta_c$$

Among treated and untreated, regress outcome $o = (stroke, bleed)$ on covariates, clinic fixed effects and $P(W|x)$

$$E(y_o|x, W = 1) = \overbrace{x_{id}\gamma_o^T + \theta_c^T}^{\mathrm{h}(x)} + \lambda_{A(x)}^{+} \cdot (P(W|x) - 1)$$

$$E(y_o|x, W = 0) = \underbrace{x_{id}\gamma^{UT} + \theta_c^{UT}}_{\mathrm{f}(x)} + \lambda_{A(x)}^{-} \cdot P(W|x)$$

Probing robustness to parametric assumptions

Relax single-index assumption:

- Currently allow index to differ by decile of stroke risk

Relax linearity assumptions in $x \quad \gamma$:

- Currently use LASSO at every stage to replace the linear function of x_{id} with a more flexible function (quadratic)
- Random forest methods (not today)

Relax linear equation modeling treatment $P(W|x)$

- Can replace linear treatment equation with logit (not today)

Relax functional form assumption in λ (not today)

- Note current model has quadratic relationship between *y* and $P(W|x)$

$$E(y_0|x) = P(W|x)E(y_0|x, W = 1) \quad + \big(1 - P(W|x)\big)E(y_0|x, W = 0)$$

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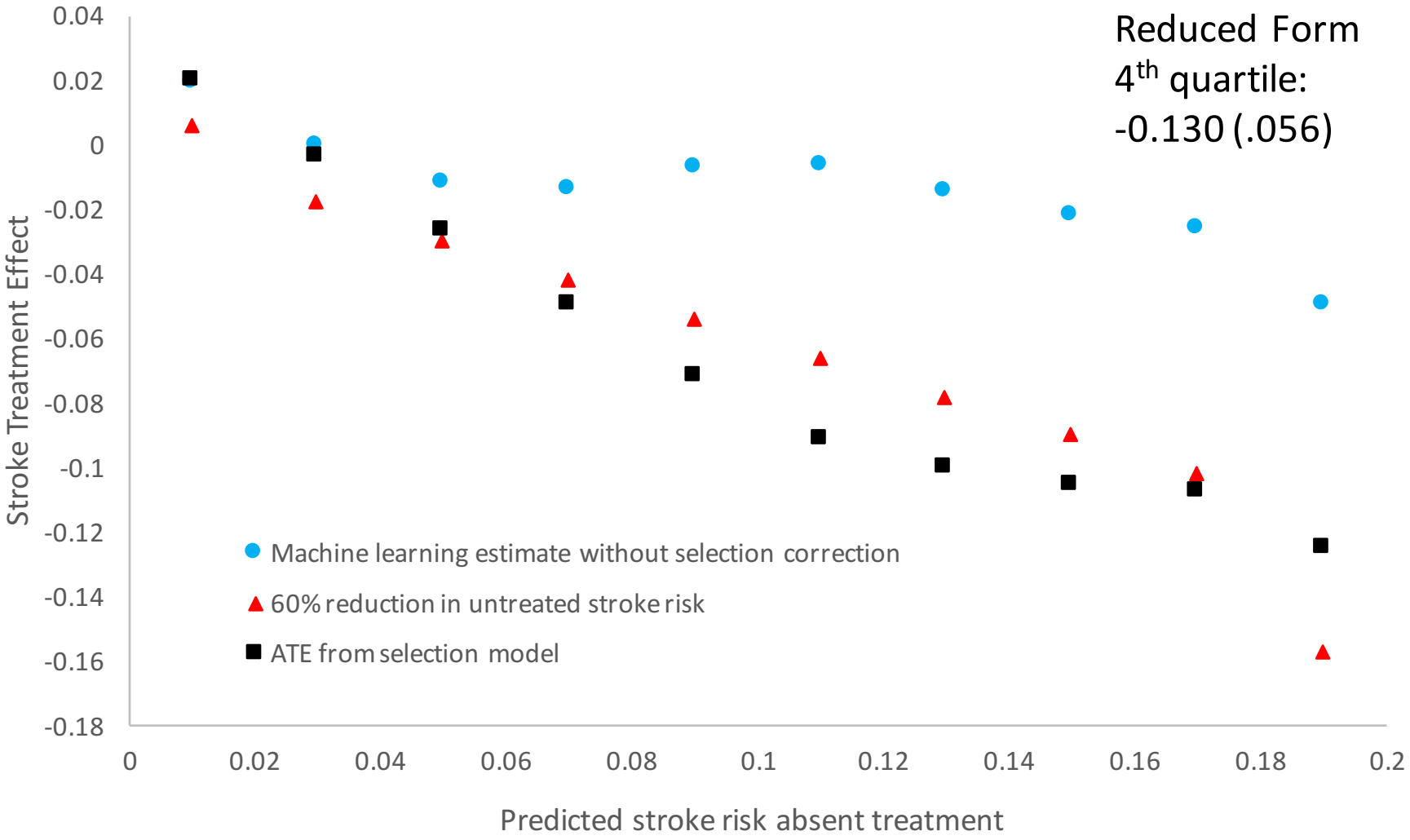
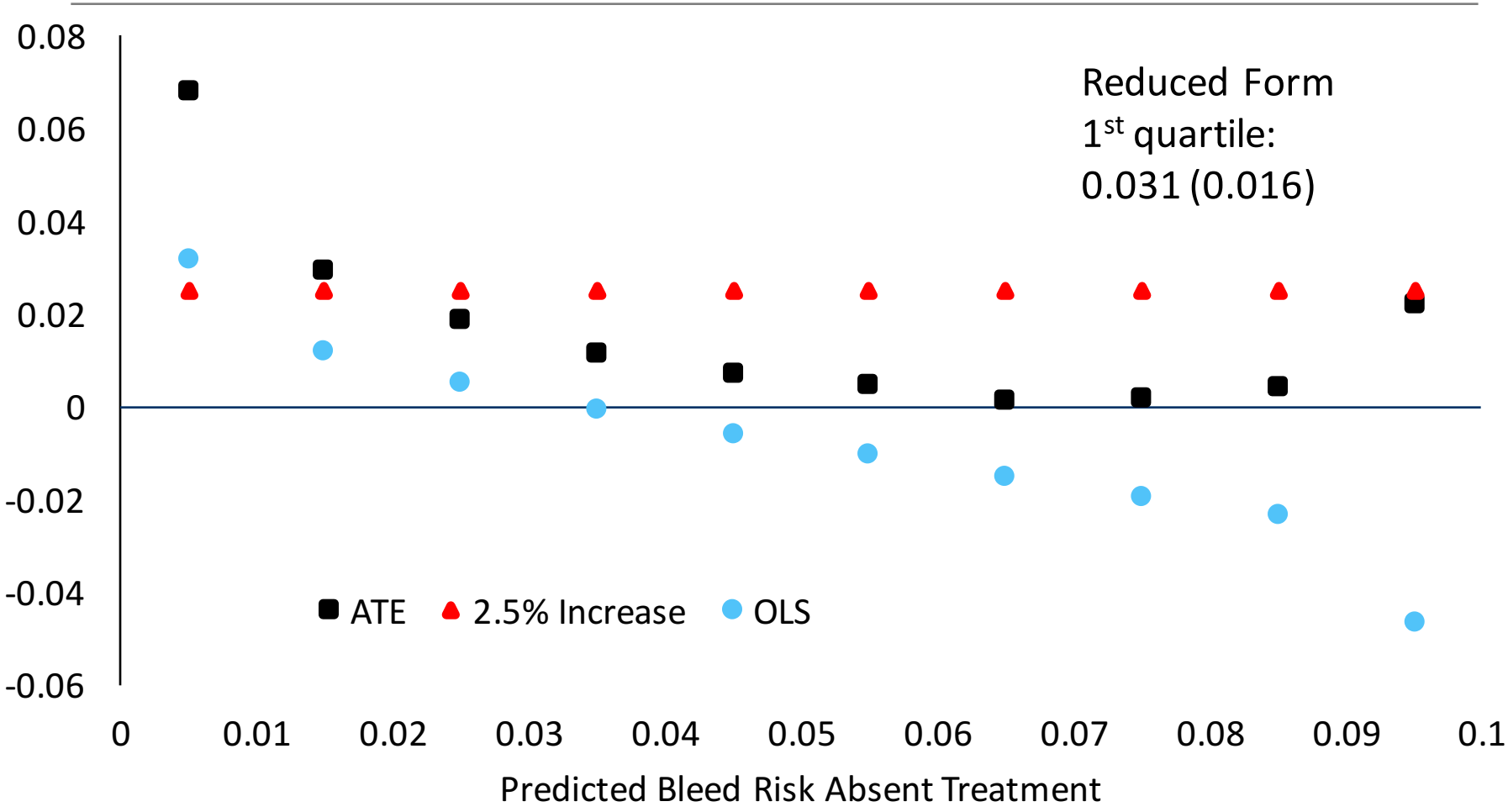
Stroke ATE vs. Stroke Risk



Bleed ATE vs. Bleed Risk



Risk and ATE by CHADS2 score

CHADS2	Observed Stroke Rate	Observed Bleed Rate	Stroke ATE	Bleed ATE
0	0.016	0.025	0.003	0.007
1	0.021	0.030	0.006	0.012
2	0.029	0.040	-0.001	0.020
3	0.050	0.053	-0.025	0.037
4	0.113	0.060	-0.079	0.043
5	0.152	0.071	-0.102	0.057
6	0.166	0.095	-0.104	0.075

LASSO: variables that predict Stroke ATE

CHADS2 (VASc)	LASSO
Congestive Heart Failure **(+)**	
Hypertension **(+)**	
Age **(+)**	Age **(+)**
Diabetes **(+)**	
Stroke or TIA in Last 3 Years **(+)**	Stroke or TIA in Last 3 Years **(+)**
Vascular Disease **(+)**	Vascular Disease **(+)**
Sex	
	Black **(+)**
	Renal Failure **(+)**
	Fall Risk **(+)**
	Neuro Disorder **(+)**

LASSO: Stroke ATE + Bleed ATE

CHADS2 (VASc)	LASSO
Congestive Heart Failure **(+)**	Congestive Heart Failure **(-)**
Hypertension **(+)**	
Age **(+)**	
Diabetes **(+)**	
Stroke or TIA in Last 3 Years **(+)**	Stroke or TIA in Last 3 Years **(+)**
Vascular Disease **(+)**	
Sex	
	Bleed History **(-)**
	Tumor **(-)**
	Chronic Pulmonary Disease **(-)**
	Neuro Disorder **(+)**

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Simulations

Scenarios we consider:

1. Status quo
2. Strict adherence to CHADS2 score
3. Optimal strict guideline – treat patients with largest value of:

$$\frac{|stroke\ ATE|}{bleed\ ATE}$$

Simulations

- We compute stroke and bleed risk for treated and untreated patients
- We compute the minimum number of possible strokes for a given number of bleeds
- We cross-validate to avoid overfitting (decide treatment given "training" data parameters, evaluate using "test" data parameters)

Min(stroke) given Bleeds

	Observed in our sample	Predicted under status quo treatment	Predicted under strict CHADS2 adherence	Predicted under optimal strict guideline
Warfarin rate	0.502	0.502	0.284	0.517
		(0.001)	(0.334)	(0.247)
Stroke rate	0.044	0.044	0.027	0.016
		0.000	(0.013)	(0.015)
Bleed rate	0.042	0.043	0.047	0.049
		(0.001)	(0.016)	(0.015)

Conclusion

- Medical researchers partly vindicated
  - Risk among untreated works well for strokes
  - But, CHADS2 variables not ideal
- Machine learning results without selection correction very biased
- Strict guidelines do better than current physician decisions
- Next step: discretionary guidelines?
- Then: randomized experiments

LASSO

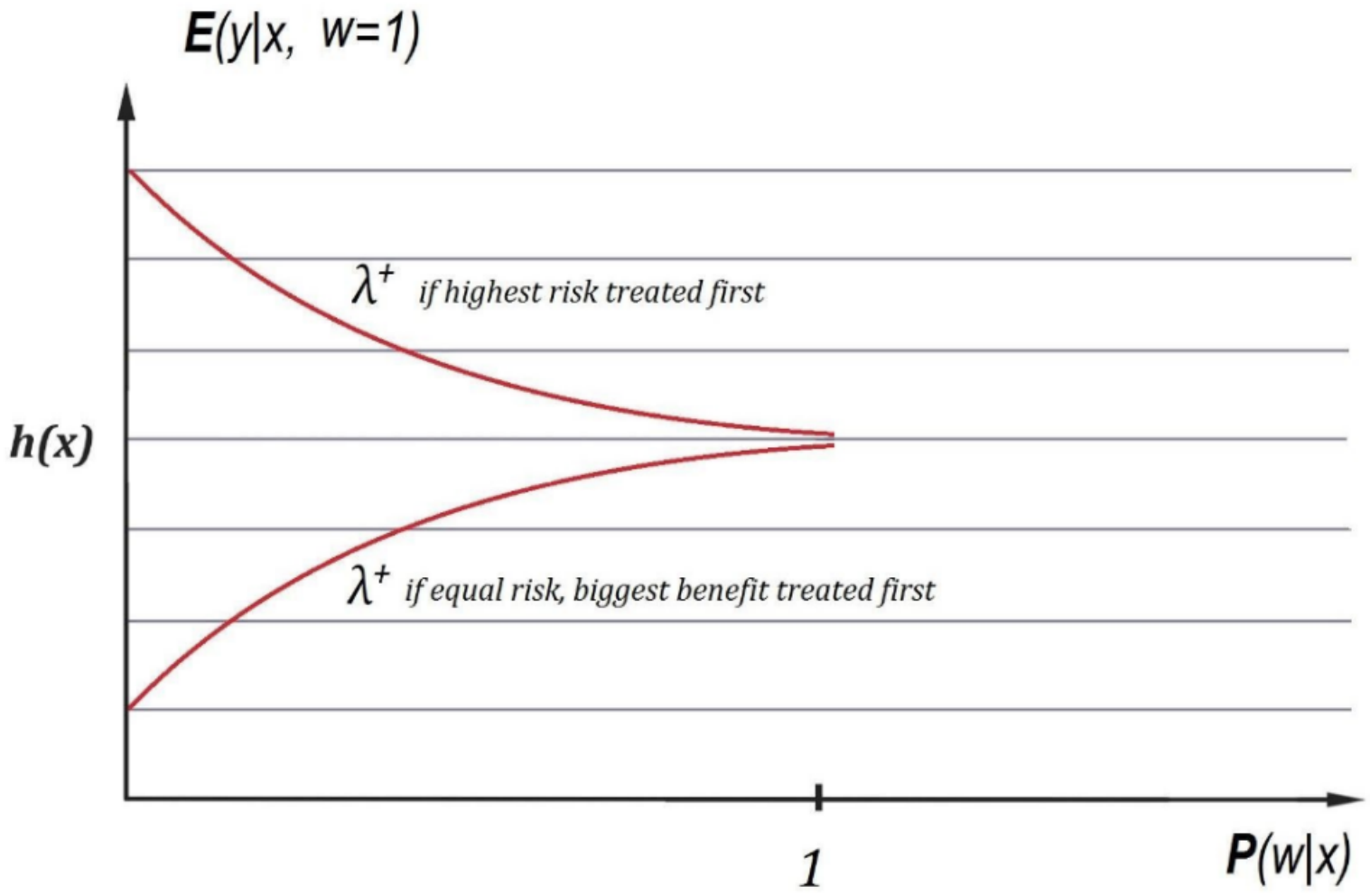
$$\hat{\beta} = argmin_b \sum_i \left(y_i - \sum_j x_{i,j} b_j \right)^2 + \lambda \sum_j |b_j| \gamma_j$$

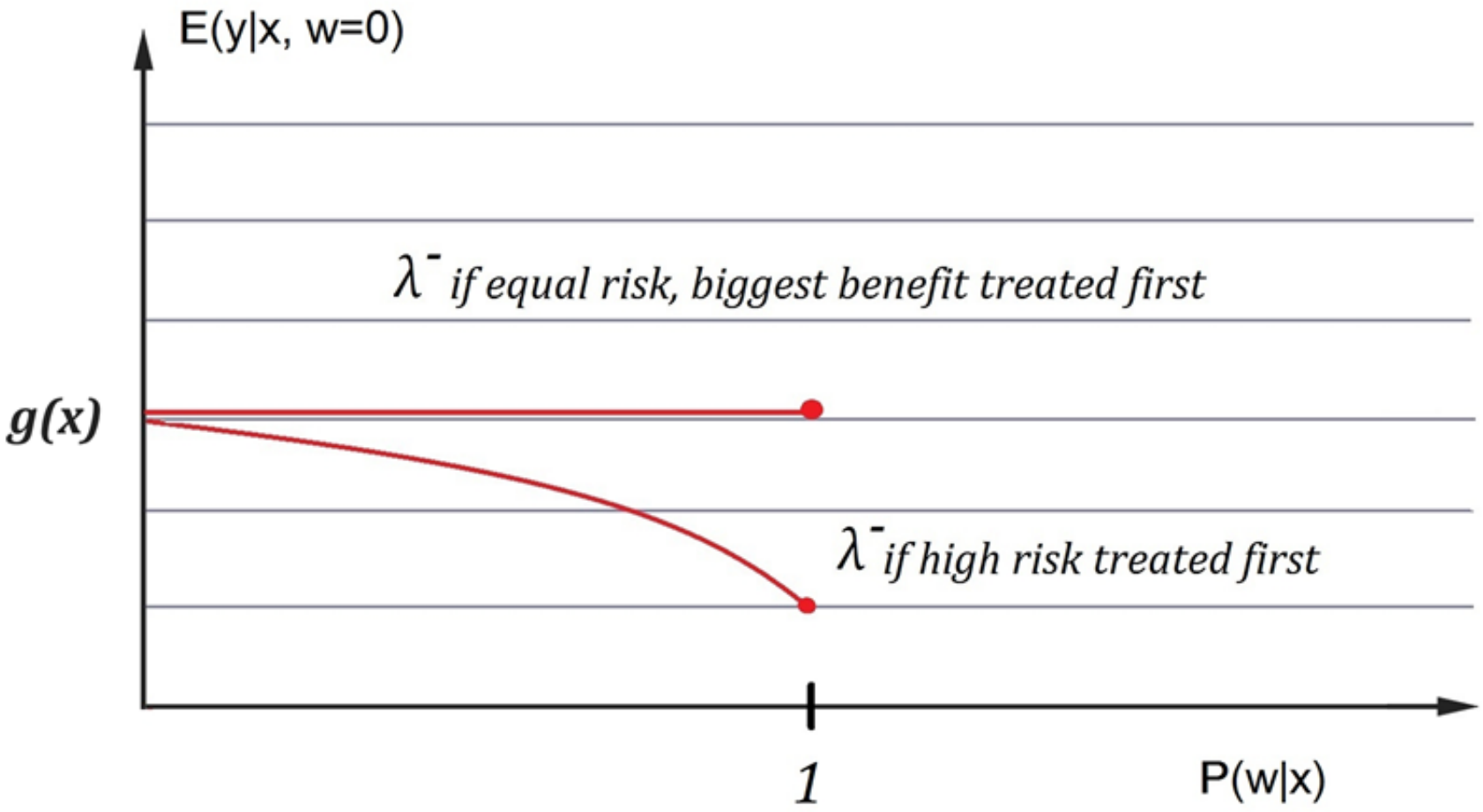
λ chosen via cross-validation to minimize MSE

Variable selection – drops many covariates

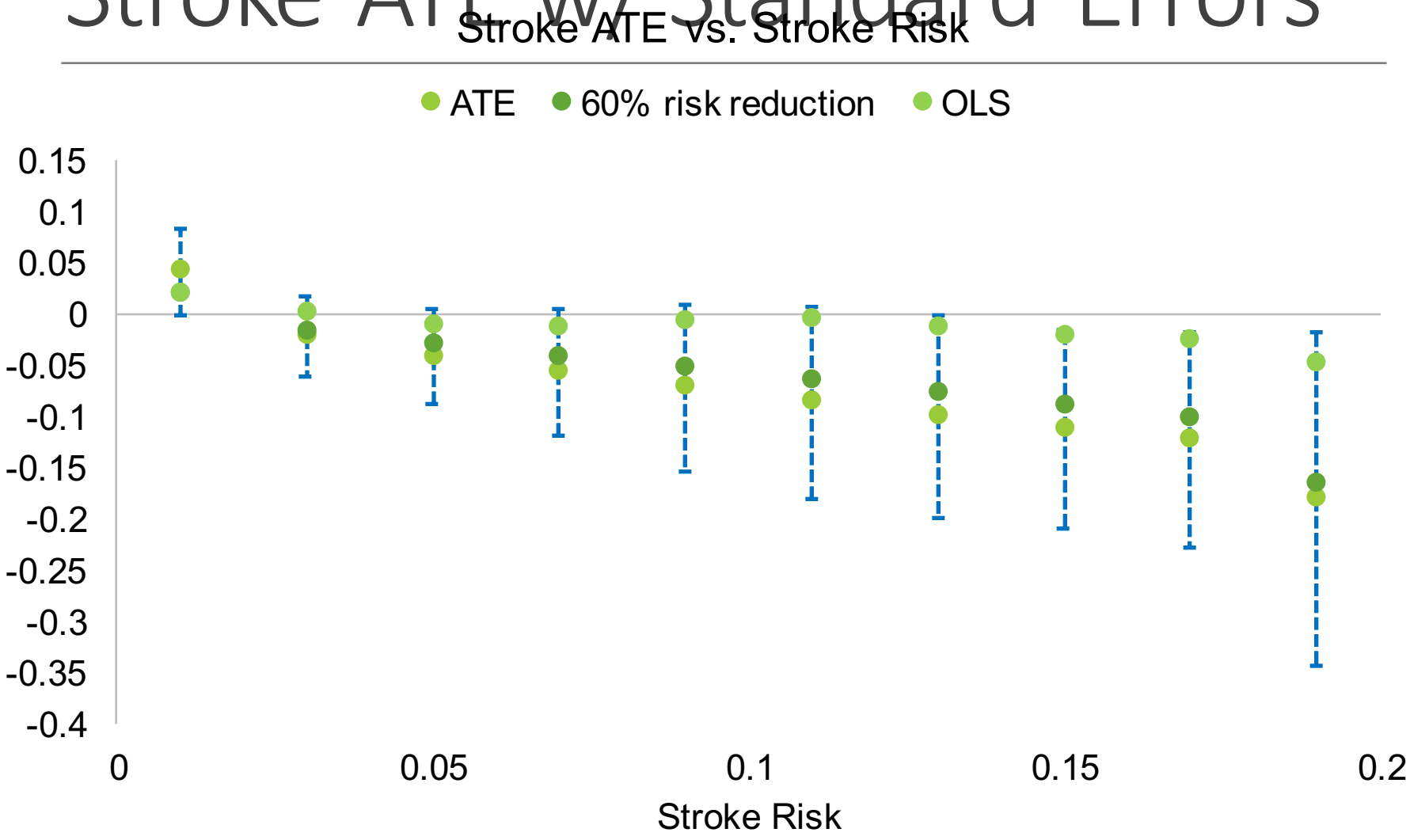
Linear, but can throw in interactions and powers of variables

Can run "post-LASSO" OLS using remaining covariates

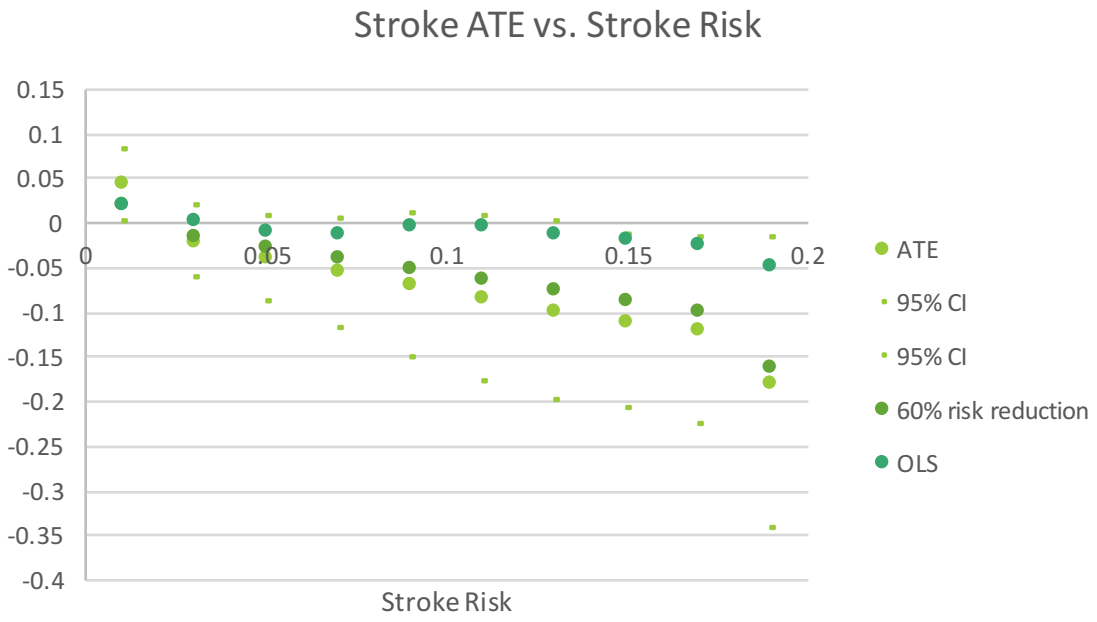

E(y|x, w=1)
h(x)
λ+ if highest risk treated first
λ+ if equal risk, biggest benefit treated first
1
P(w|x)


E(y|x, w=0)
λ- if equal risk, biggest benefit treated first
g(x)
λ- if high risk treated first
1
P(w|x)

Stroke ATE w/ Standard Errors



Stroke ATE w/ Standard Errors



Results so far

CHADS score impacted Warfarin prescriptions

Steep drop for CHADS score of 0 and 1. Increase for CHADS score >= 2

Maybe some reduction in strokes?

Need for Structural Model

We want a structural model so that we can:

1) Estimate heterogeneous treatment

2) Allow treatment effects to reflect selection on unobservables (diminishing returns if more patients tested with same x's)

3) Deal with potential threats to validity of IV – violations of monotonicity

Model

$$Y_{id}(0) = f(x) + \eta_{0id}$$
$$Y_{id}(1) = h(x) + \eta_{1id}$$

Doctors treat if:

$$B_{id} = g^*(x, \theta_d) + \eta'_{id} > 0$$

Assume uniform error to get linear model

This is w.l.o.g for flexible g^*, see Vytlacil (2002)

$Y = stroke\ or\ bleed$

$$E(Y|x, W = 1) = h(x) + \lambda^{+}(P(W|x))$$

$$E(Y|x, W = 0) = f(x) + \lambda^{-}(P(W|x))$$

$$\lambda^{+}(1) = \lambda^{-}(0) = 0$$
$$ATE = g(x) = h(x) - f(x)$$
$$MTE = g(x) + \Delta\lambda(P)$$

$$E(Y|x, W) = [g(x) + \Delta\lambda(P)]W + [f(x) + \lambda^{-}(P)]$$

Optimization Problem

$$Min_{P(W|x)} E(stroke)\ s.t.\ E(bleed) = K$$

$$E(outcome)$$
$$= \sum_i \{P(W|x)[h(x) + \lambda^+(P(W|x)]$$
$$+(1 - P(W|x))[f(x) + \lambda^-\big(P(W|x)\big)]\}$$

Are other variables misweighted?

Assuming (for the moment) treatment effects are proportional to risk,

Are doctors treating the patients at highest risk of stroke?

For a given increase in bleed risk, are docs treating patients with the largest increase in stroke risk?

	Coefficients (times 100)					
	y = Warfarin		y = Bleed		y = Stroke	
	(1)		(2)		(3)	
CHADS: Age	-6.11	***	0.25	***	0.48	***
	(0.21)		(0.08)		(0.08)	
CHADS: Hypertension	4.46	***	0.28	***	0.48	***
	(0.26)		(0.10)		(0.10)	
CHADS: Diabetes	3.76	***	0.13	*	0.21	***
	(0.22)		(0.08)		(0.08)	
CHADS: Heart Disease	2.02	***	0.10		0.84	***
	(0.27)		(0.10)		(0.10)	
CHADS: Stroke Hist	3.65	***	9.02	***	0.41	***
	(0.29)		(0.11)		(0.11)	
Pulmonary Disease	0.24		-0.17	**	0.83	***
	(0.22)		(0.08)		(0.08)	
Tumor	-1.89	***	0.04		0.89	***
	(0.27)		(0.10)		(0.10)	
Ulcer	-1.37		0.41		1.98	***
	(1.28)		(0.48)		(0.47)	
Electrolyte Disorder	-1.70	***	0.64	***	1.13	***
	(0.33)		(0.12)		(0.12)	

Relevant Health Literature

Garber and Skinner (2008) – flat of the curve or wrong production function?

Finkelstein, Gentzkow and Williams (2014), Molitor (2012) – provider behavior matters, Cutler, Skinner, Stern and Wennberg

Chandra and Staiger (2011) – Roy model for estimating treatment effects (applying Heckman and Vytlacil)

Currie and Macleod (2013) – do docs target C-sections to patients who benefit?

From Abaluck and Agha (2015)

Table 2: Summary statistics illustrating potential misweighting of risk factors

	A. Fraction tested	*B. Test yield*
Selected candidates for under-weighting		
Prostate cancer (CCW)	0.0370	0.1019
No prostate cancer (CCW)	0.0380	0.0677
Black	0.0313	0.0851
Non-black	0.0385	0.0682
History of PE	0.0726	0.1881
No history of PE	0.0378	0.0686
History of deep vein thrombosis	0.0507	0.1656
No history of deep vein thrombosis	0.0378	0.0685
Prior hospital visit within 30 days	0.0465	0.1976
No prior hospital visit within 30 days	0.0377	0.0656
Selected candidates for over-weighting		
Chronic obstructive pulmonary disease (CCW)	0.0466	0.0524
No chronic obstructive pulmonary disease (CCW)	0.0360	0.0742
Atrial fibrillation	0.0742	0.0520
No atrial fibrillation	0.0388	0.0713
Ischemic heart disease	0.0376	0.0566
No ischemic heart disease	0.0382	0.0786

Now much better data…

See nearly everything the doctor sees

Can reconstruct guidelines

Can observe (sort of) whether doctor uses guidelines

Will show effectively random assignment of patients to physicians which we can use to estimate treatment effects

Model w/ Subscripts

$$E\left(Y_{idc}^{s,b} \middle| x_{idc}, c, d, W_{idc} = 1\right)$$
$$= g_1^{s,b}(x_{id}, \alpha_{1c}) + \lambda^{s,b+}(P(W_{idc} = 1 | x_{idc}, c, d))$$

$$E\left(Y_{idc}^{s,b} \middle| x_{idc}, c, d, W_{idc} = 0\right)$$
$$= g_0^{s,b}(x_{id}, \alpha_{0c}) + \lambda^{s,b-}(P(W_{idc} = 1 | x_{idc}, c, d))$$

$$\lambda^{+}(1) = \lambda^{-}(0) = 0$$
$$ATE = \Delta g(x_{id}, \alpha_c) = g_1(x_{id}, \alpha_{1c}) - g_0(x_{id}, \alpha_{0c})$$
$$MTE = \Delta g(x_{id}, \alpha_c) + \Delta\lambda(P)$$

Optimization Problem

$$Min_{P(W|x_{id})} E(stroke)\ s.t. E(bleed) = K$$

$$E(outcome)$$
$$= \sum_i \{P(W|x_{id})[g_1^{s,b}(x_{id}, \alpha_c) + \lambda^+(P(W|x_{id})]$$
$$+(1 - P(W|x_{id}))[g_0^{s,b}(x_{id}, \alpha_c) + \lambda^-\big(P(W|x_{id})\big)]\}$$

Derivation

$$Y_{id}(0) = f(x) + \eta_{0id}$$
$$Y_{id}(1) = h(x) + \eta_{1id}$$

Doctors treat if:

$$B_{id} = g^*(x) + \eta'_{id} > \tau_d$$

Almost w.l.o.g! (assume τ_d additively separable so we can implement our IV strategy)

Derivation

$$E(Y(1)|W = 1) = h(x) + E(\eta_j|g^*(x) - \tau_d > -\eta'_{id})$$

$$P(W = 1|x) = H(g^*(x) - \tau_d)$$

$$E(Y(1)|W = 1) = h(x) + E\left(\eta_j|H^{-1}\left(P(W = 1|x)\right) > -\eta'_{id}\right)$$
$$= h(x) + \lambda^+(P(W = 1|x))$$

LASSO

$$\hat{\beta} = argmin_b \sum_i \left(y_i - \sum_j x_{i,j} b_j \right)^2 + \lambda \sum_j |b_j| \gamma_j$$

λ chosen via cross-validation to minimize MSE

Variable selection – drops many covariates

Linear, but can throw in interactions and powers of variables

Can run "post-LASSO" OLS using remaining covariates

IV Estimates

Now the model is:

$$E(Y_i|X_i) = g(X_i)W_i + f(X_i)$$

Gives earlier model if:

$$g^{stroke}(X_i) = -0.6f^{stroke}(X_i)$$
$$g^{bleed}(X_i) = .02$$

No unobservable heterogeneity in treatment effects

IV Estimates

$$Y_i = g(X_i)W_i + f(X_i) + e_i$$

Athey-Imbens (2015) gives a trick to estimating this with a binary W_i from randomized experiment

Assume further that:

$$W_i = \gamma Z_i + v_i$$

Then:

$$E(Y_i|Z_i) = g(X_i)(\gamma Z_i) + f(X_i)$$

IV Estimates

We extend this to work with IV models

Define: $\widetilde{Y}_i = Y_i \frac{\gamma Z_i - E(\gamma Z_i | X_i)}{E\left((\gamma Z_i)^2 \middle| X_i\right) - \left(E(\gamma Z_i | X_i)\right)^2}$

This transformation has the convenient property that: $\mathrm{E}\left(\widetilde{Y}_i \middle| X_i\right) = g(X_i)$

So we can estimate $g(X_i)$ by applying LASSO to this transformation

IV Estimates

Once we have an estimate $\hat{g}(X_i)$, we can easily compute:

$$f(X_i) = E(Y_i - \hat{g}(X_i)W_i|X_i)$$

Again using LASSO methods

And then we have what we wanted – an estimate of the stroke risk for every patient if they are treated and if they are untreated

IV Estimates

Want to minimize strokes for given bleeds, we compute for every patient the ratio of treatment effects $g^{stroke}(X_i)/g^{bleed}(X_i)$

Assign Warfarin to patients with largest value of this ratio until predicted bleeds = actual bleeds

Simulation: IV Model

	Actual	Simulated	CHADS	Doc	OLS	LASSO
# of Variables	-	-	5	51	51	5
% Warfarin	53.6	53.6	49.1	55.7	57.1	64.3
% Stroke	3.73	3.76	3.31	3.54	3.61	2.91
% Bleed	3.44	3.51	3.51	3.51	3.51	3.51
Strokes Prevented			12.0%	5.9%	4.0%	22.6%

CHADS2 (VASc)	LASSO
Congestive Heart Failure	Congestive Heart Failure
Hypertension	
Age >= 75	Age >= 75
Diabetes	
Stroke or TIA in Last 3 Years	
Vascular Disease	Vascular Disease
Age 65-74	
Sex	
	Alcoholism
	Ulcer

First-stage

The first stage of the original jackknife estimator is .0392 (.0038), compared to 1.188 (.0774) for the EB estimator

The nR^2 (a measure of the power of the IV) increases from 99.5 to 249 (10 is the threshold for weak instruments)