The Role of Study Design to Reduce the Potential for Confounding

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Potential Conflicts of Interest

- R01 AG023178 (PI) and R01 AG042845 (Co-I), National Institute on Aging
- R01 CA174453 (Co-I), National Cancer Institute
- IP2PI000075 (PI), Patient Centered Outcomes Research Institute (PCORI)
- AstraZeneca (PI), Amgen (Co-I)
- Center for Pharmacoepidemiology (GlaxoSmithKline, UCB BioSciences, Merck)
- All to University of North Carolina at Chapel Hill

Confounding by Indication

- Good prescribing leads to confounding of drug effects on intended outcomes
- More severe disease more likely to
  - Be treated (with higher doses)
  - Have higher risk of outcomes (we like to prevent)
- Assessment of severity of disease often difficult
- Intractable confounding
- Drug looks BAD compared with **NON-USERS**!
  - E.g., increased asthma mortality with beta-agonists

Confounding by Frailty in Population Based PE Studies

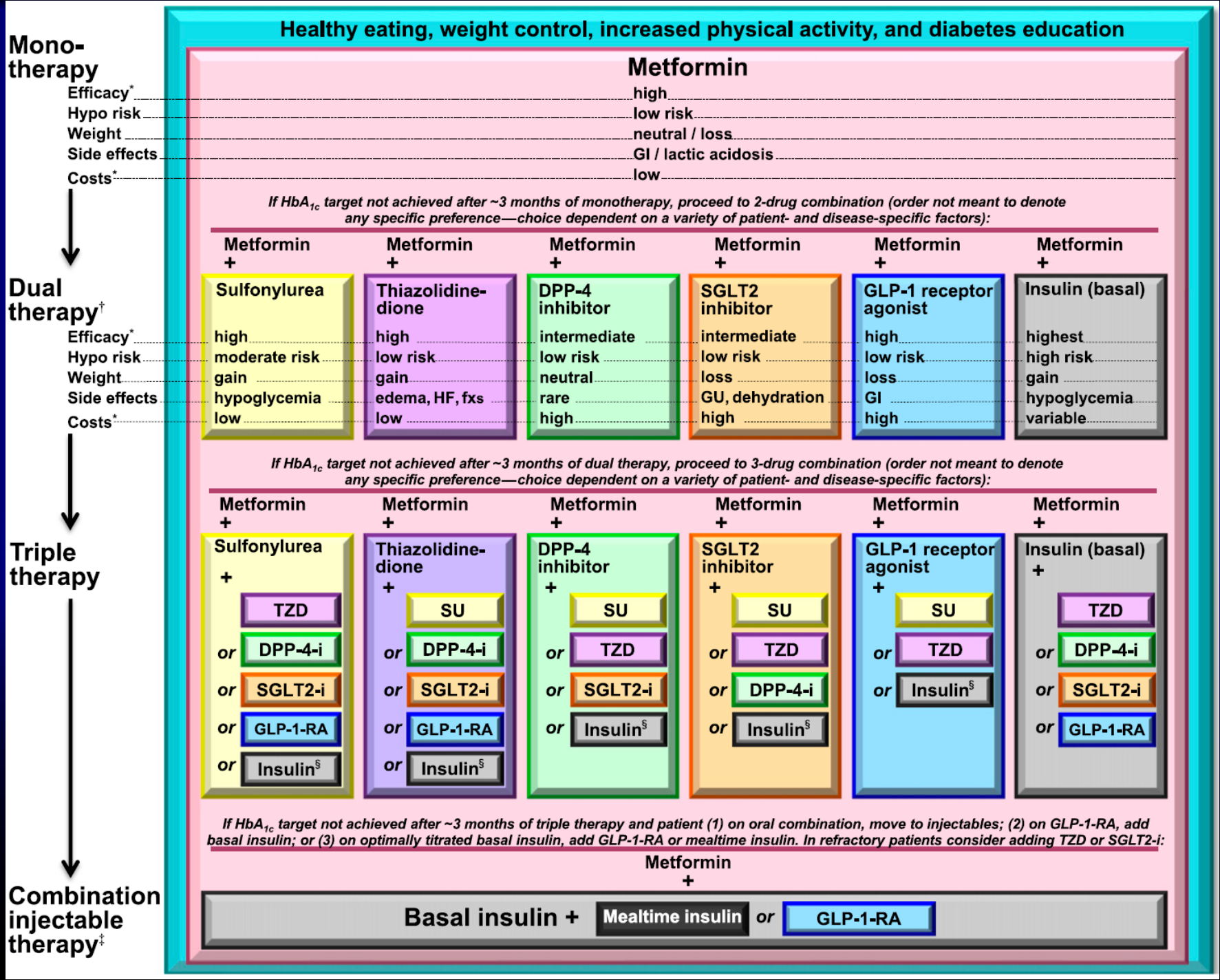
- Individuals close to death are
  - Less likely to receive preventive treatments
    - E.g., statins, flu vaccination
  - More likely switched to palliative treatments
    - E.g., opiates instead of NSAIDs
  - More likely to receive certain classes of drugs
    - E.g., loop diuretics vs. other diuretics
- Paradoxical drug mortality associations
- Drug looks GOOD compared with **NON-USERS**!

Intractable Confounding?

- We cannot (well) measure indication nor frailty
- Need other means to control for confounding
  - Randomization, but clearly not feasible to get timely answers for ALL relevant drug related research questions
  - Restriction, very powerful tool to address confounding (e.g., Schneeweiss et al., Med Care 2007)
- Can we (implicitly) restrict to (same) indication?
  - Potential to reduce confounding by indication AND frailty
- Compare treatment alternatives with equipoise for same indication
  - Guideline, clinical practice
- New user, active comparator design

So Much for the Theory, but Does it Really Work?

- Non-selected examples from recent studies on antidiabetics @ UNC
  - Guideline (Diab Care 2015;38:140-149)
  - Metformin versus Sulfonylurea
  - DPP-4 versus TZD/sulfonylurea
  - Glargine versus NPH insulin


Healthy eating, weight control, increased physical activity, and diabetes education
Mono-therapy
Metformin
Efficacy*
high
Hypo risk
low risk
Weight
neutral / loss
Side effects
GI / lactic acidosis
Costs*
low
If HbA1c target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):
Dual therapy†
Metformin + Sulfonylurea
Efficacy* high
Hypo risk moderate risk
Weight gain
Side effects hypoglycemia
Costs* low
Metformin + Thiazolidine-dione
high
low risk
gain
edema, HF, fxs
low
Metformin + DPP-4 inhibitor
intermediate
low risk
neutral
rare
high
Metformin + SGLT2 inhibitor
intermediate
low risk
loss
GU, dehydration
high
Metformin + GLP-1 receptor agonist
high
low risk
loss
GI
high
Metformin + Insulin (basal)
highest
high risk
gain
hypoglycemia
variable
If HbA1c target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):
Triple therapy
Metformin + Sulfonylurea + TZD or DPP-4-i or SGLT2-i or GLP-1-RA or Insulin§
Metformin + Thiazolidine-dione + SU or DPP-4-i or SGLT2-i or GLP-1-RA or Insulin§
Metformin + DPP-4 inhibitor + SU or TZD or SGLT2-i or Insulin§
Metformin + SGLT2 inhibitor + SU or TZD or DPP-4-i or Insulin§
Metformin + GLP-1 receptor agonist + SU or TZD or Insulin§
Metformin + Insulin (basal) + TZD or DPP-4-i or SGLT2-i or GLP-1-RA
If HbA1c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-i:
Combination injectable therapy‡
Metformin +
Basal insulin + Mealtime insulin or GLP-1-RA

Metformin

- First line treatment pts. with type 2 diabetes
- Reduction of cancer incidence and mortality?
  - Breast, colon and rectum, liver, pancreas, stomach, prostate, esophagus, etc?
  - Some biology
- Time related biases (Suissa & Azoulay 12, 14)
- Active comparator?
  - Guideline: none
  - Empirically: sulfonylureas

Initiation of Metformin vs. Sulfonylurea, US Medicare

Table	Metformin	Sulfonylureas
Total	36367 (100.0)	11730 (100.0)
Median of Age (IQR)	72.0 (68.0-78.0)	76.0 (70.0-84.0)
Race		
White	28855 (79.3)	9088 (77.5)
African American	3858 (10.6)	1590 (13.6)
Others	3654 (10.0)	1052 (9.0)
Comorbidity		
Benign Breast Disease	1284 (3.5)	290 (2.5)
Benign neoplasm of breast	55 (0.2)	15 (0.1)
Chronic Obstructive Pulmonary Disease	2737 (7.5)	1136 (9.7)
Congestive Heart Failure	3199 (8.8)	2036 (17.4)
Ischemic Heart Disease	6522 (17.9)	2987 (25.5)
Hypertension	28332 (77.9)	9139 (77.9)
Osteoporosis	4069 (11.2)	1259 (10.7)

Jin-Liern Hong et al., submitted

Initiation of Metformin vs. Sulfonylurea, US Medicare

Table	Metformin	Sulfonylureas
Medications		
Estrogen	2232 (6.1)	491 (4.2)
Progestin	262 (0.7)	45 (0.4)
Statins	20268 (55.7)	5413 (46.1)
Bisphosphonates	4384 (12.1)	1184 (10.1)
ACE Inhibitors	13715 (37.7)	4354 (37.1)
ARBs	7762 (21.3)	2253 (19.2)
Beta Blockers	14412 (39.6)	4978 (42.4)
Antidepressants	10313 (28.4)	3385 (28.9)
Digoxin	1682 (4.6)	998 (8.5)
Calcium Channel Blockers	10479 (28.8)	3676 (31.3)
Loop Diuretics	5703 (15.7)	2987 (25.5)
Non-Loop Diuretics	14747 (40.6)	3968 (33.8)

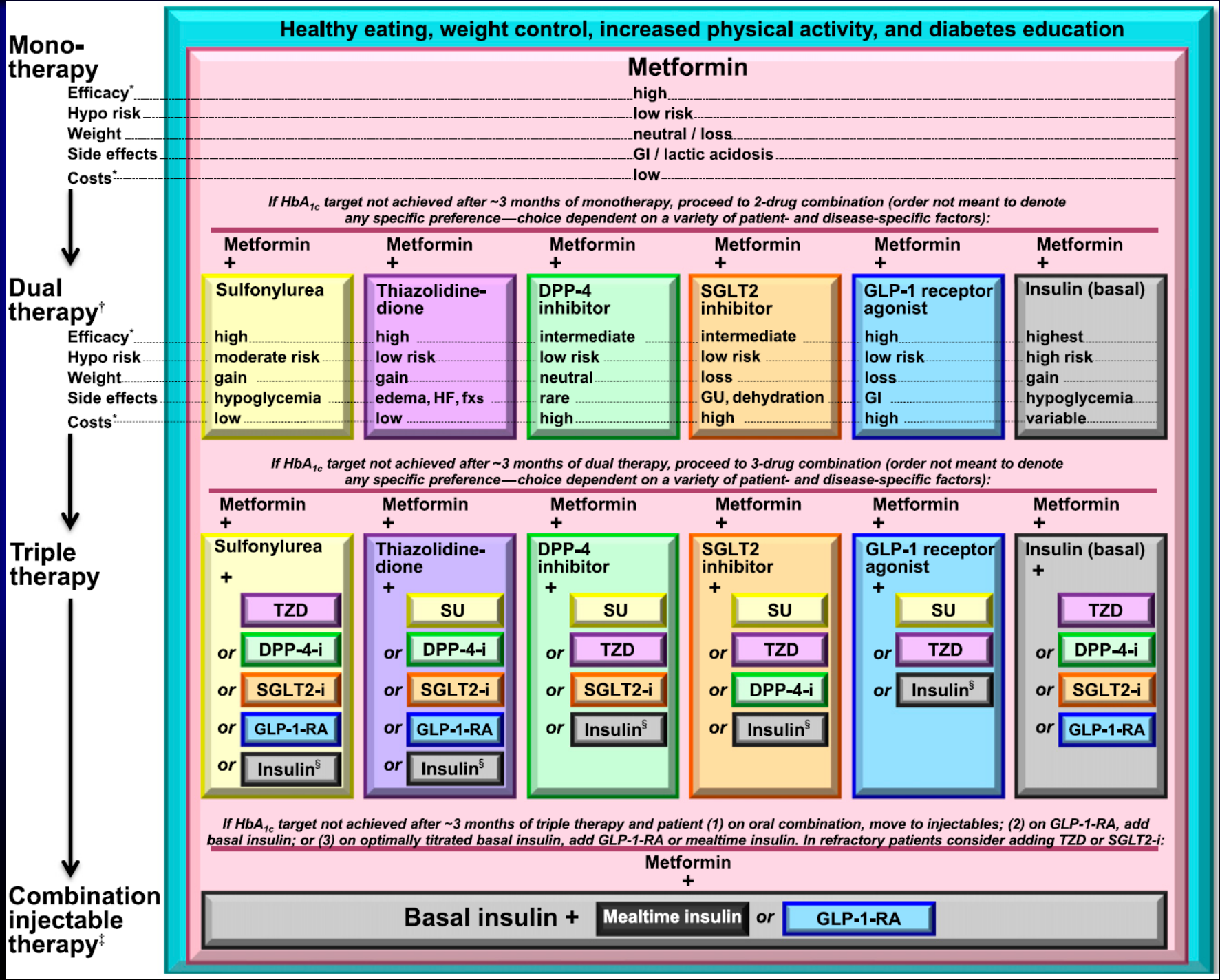
Metformin vs. Sulfonylurea: Medicare Current Beneficiary Survey

Table 3. Characteristics in Metformin and Sulfonylureas at Baseline in MCBS 2006-2009

	MET	SUL
Total	118 (100.0)	79 (100.0)
Median Age (IQR)	74.0 (70.0-80.0)	78.0 (75.0-84.0)
Race		
White	89 (75.4)	59 (74.7)
Other	29 (24.6)	20 (25.3)
Median of BMI (IQR)	29.9 (25.6-34.0)	28.6 (25.1-33.1)
Mean of BMI (Stdev)	30.5 (6.5)	29.9 (6.9)
BMI Category*		
25	24 (20.3)	18 (22.8)
25-30	35 (29.7)	30 (38.0)
30+	58 (49.2)	29 (36.7)
Smoking Status*		
Never	61 (51.7)	48 (60.8)
Ever Smoking	57 (48.3)	28 (35.4)

Dipeptidyl-peptidase-4 inhibitors

- Introduced (US) in 2006
- Improve glycemic control in type 2 diabetics
- Sitagliptin first in class, saxagliptin (2008), linagliptin (2011) and alogliptin (2012)
- P.O., good tolerability, body-weight neutrality
- 2009: FDA safety communication for acute pancreatitis
- 2011: pancreatic cancer in FAERS (ROR=2.7)
- 2013: increased pancreatic cell proliferation and dysplasia (autopsy study)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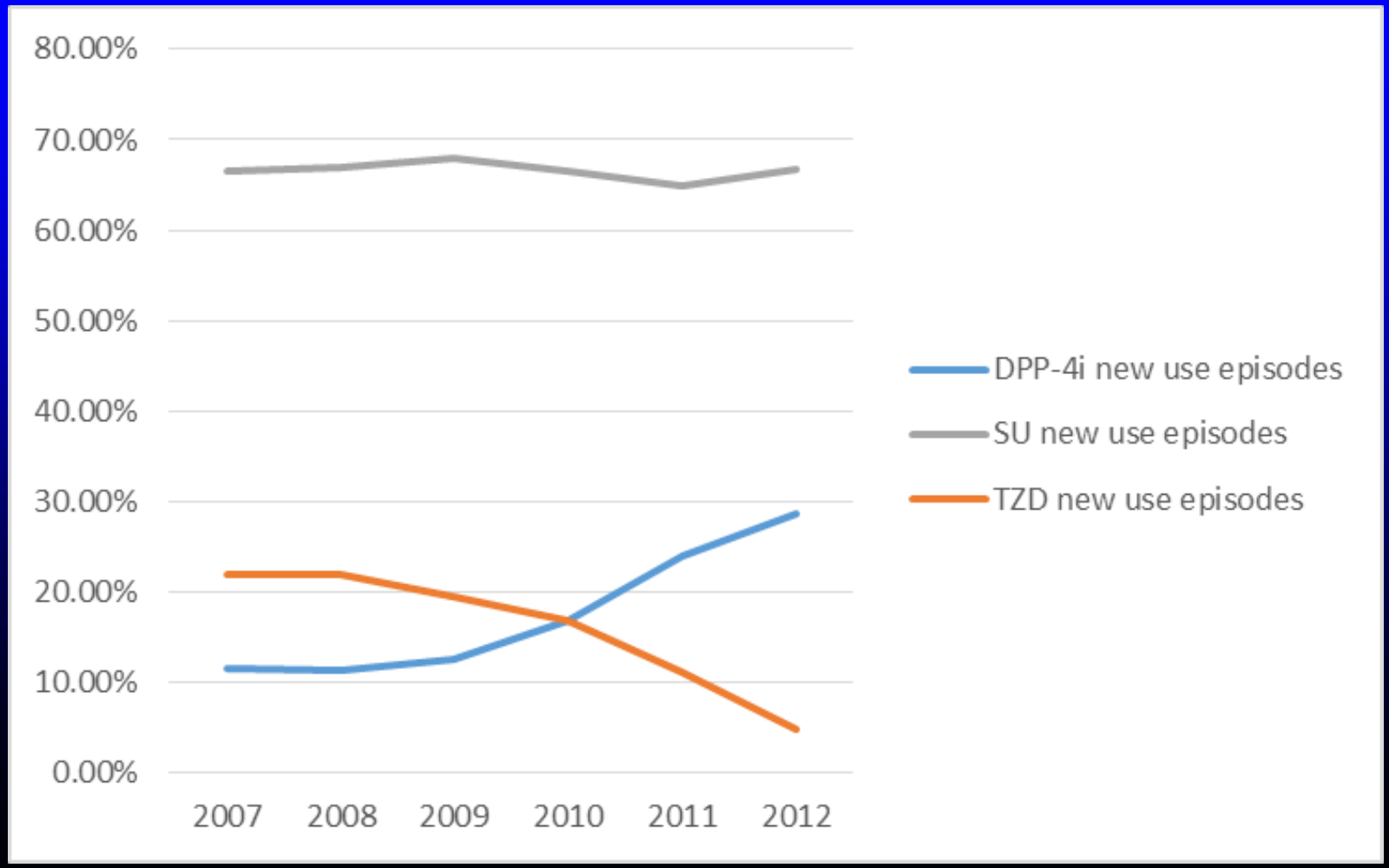
Time Trends in Initiation of Oral Antidiabetics: US Medicare



Gokhale et al., unpublished results

Dipeptidyl-peptidase-4 inhibitors

Gokhale et al., Diabet Obes Metab 2014	DPP-4 inhibitors (N = 29 366)		TZD (N = 26 332	
	n	%	n	%
Mean (s.d.) age, years	75.61 (7.10)		74.64 (6.70)	
66 – 75 years	16 407	55.87	16 100	61.14
76 – 85 years	9782	33.31	8130	30.87
≥86 years	3177	10.82	2102	7.98
Male	10 590	36.06	10 609	40.29
White	22 245	75.75	18 628	70.74
Black	3059	10.42	3140	11.92
Other	4062	13.83	4564	17.33
Comorbidities§				
Connective tissue disease	9966	33.94	7763	29.48
Depression	4709	16.04	3712	14.10
Chronic obstructive pulmonary disease	5595	19.05	3999	15.19
Chronic kidney disease	5790	19.72	4031	15.31
Congestive heart failure	7740	26.36	4373	16.61
Diabetic neuropathy	6478	22.06	4813	18.28
Diabetic nephropathy	2660	9.06	1954	7.42
Diabetic retinopathy	5260	17.91	4432	16.83
Diabetic cataract	83	0.28	73	0.28
Gastrointestinal disorders	256	0.87	208	0.79
Alcohol use¶	316	1.08	258	0.98
Tobacco use¶	78	0.27	59	0.22
Pancreatitis	318	1.08	243	0.92

Dipeptidyl-peptidase-4 inhibitors

	DPP-4 inhibitors (N = 29 366)		TZD (N = 26 332	
	n	%	n	%
Medication use**				
Insulin	5409	18.42	4445	16.88
Metformin	16 805	57.23	14 282	54.24
Sulfonylureas	13 530	46.07	11 352	43.11
Angiotensin-converting enzyme inhibitors	10 907	37.14	9899	37.59
Angiotensin receptor blockers	8184	27.87	5982	22.72
Statins	19 331	65.83	15 466	58.73
Loop diuretics	8294	28.24	5025	19.08
Other diuretics	7831	26.67	6861	26.06
β-blockers	15 350	52.27	11 288	42.87
Calcium channel blockers	10 334	35.19	8440	32.05
Healthcare utilization§				
Blood tests	2675	9.11	2261	8.59
Lipid panel	25 483	86.78	22 105	83.95
Influenza vaccinations	16 325	55.59	13 427	50.99

Gokhale et al., Diabet Obes Metab 2014

Insulin Glargine

- Human insulin analogue
- Implicated with increased risk for cancer (any) in large cohort study from Germany
- Some lab evidence
- Insulin mostly used in type 2 diabetics not controlled by 1st and 2nd line oral antidiab.
- Clincal alternative: human NPH insulin
- New user, active comparator design

Confounding Control by Design

	Actual cohorts		Effect on channeling, OR (95% CI)†
	Glargine	NPH	
n	43,306	9,147	
Age (years), mean (SD)	61.3 (14.0)	58.9 (17.2)	1.001 (0.999–1.003)
Sex			
Male	20,369 (47.0)	3,611 (39.5)	1.29 (1.22–1.37)
Female	22,937 (53.0)	5,536 (60.5)	1.00 (reference)
Comorbidities			
Congestive heart failure	8,074 (18.6)	1,645 (18.0)	1.01 (0.93–1.09)
Diabetic nephropathy	11,432 (26.4)	2,345 (25.6)	0.90 (0.84–0.95)
Diabetic neuropathy	9,998 (23.1)	2,110 (23.1)	0.86 (0.81–0.91)
Diabetic retinopathy	11,613 (26.8)	2,364 (25.8)	0.94 (0.89–1.00)
Hypertension	35,314 (81.6)	6,842 (74.8)	1.13 (1.06–1.20)
Pulmonary infection	10,642 (24.6)	2,344 (25.6)	0.98 (0.92–1.05)
Health care use			
Hospitalizations (any reason)			
1	8,961 (20.7)	1,922 (21.0)	1.17 (1.07–1.29)
2	3,144 (7.3)	662 (7.2)	1.15 (1.03–1.28)
≥3	2,512 (5.8)	515 (5.6)	1.25 (1.11–1.42)
Days in hospital (any reason)			
1–2	2,794 (6.5)	618 (6.8)	0.92 (0.82–1.04)
3–5	4,251 (9.8)	913 (10.0)	0.95 (0.86–1.06)

OK, But What About BMI?

- BMI probably strongest predictor for adding insulin in T2DM and RF for some cancers
- External validation study
  - Estimate **independent** effect of BMI on prescribing glargine VERSUS NPH
  - At time of initiation (same indication)
  - Using EMR data (here: MGH, Ochsner)
- Use known effect of BMI on cancer risk to estimate confounding if BMI unbalanced
- Assumption: BMI effect on treatment choice transportable

Limiting Confounding by Design

Table 4—*Effect of BMI on channeling between initiating glargine versus initiating NPH: external validation studies*

	Glargine	NPH
MGH		
n	574	412
BMI (kg/m^2), mean ± SD*	32.7 ± 7.53	32.4 ± 8.43
BMI (kg/m^2), *n* (%)		
<19	4 (0.7)	8 (1.9)
19 to <25	77 (13.4)	67 (16.3)
25 to <30	150 (26.1)	105 (25.5)
30 to <35	146 (25.4)	104 (25.2)
35 to <40	114 (19.9)	64 (15.5)
40 to <45	45 (7.8)	36 (8.7)
≥45	38 (6.6)	28 (6.8)

Sturmer et al. Diabetes Care 2013

Some Differences Remain!

	Actual cohorts		Effect on channeling, OR (95% CI)†
	Glargine	NPH	
n	43,306	9,147	
Age (years), mean (SD)	61.3 (14.0)	58.9 (17.2)	1.001 (0.999–1.003)
Sex			
Male	20,369 (47.0)	3,611 (39.5)	1.29 (1.22–1.37)
Female	22,937 (53.0)	5,536 (60.5)	1.00 (reference)
Metformin	27,347 (63.2)	4,544 (49.7)	1.26 (1.19–1.33)
Niacin	810 (1.9)	108 (1.2)	1.14 (0.93–1.41)
Nonloop diuretics	7,684 (17.7)	1,397 (15.3)	1.04 (0.97–1.11)
Oral contraceptives	593 (1.4)	317 (3.5)	0.71 (0.56–0.90)
Other diabetes drugs	9,416 (21.7)	891 (9.7)	1.87 (1.73–2.01)
Progestins	407 (0.9)	145 (1.6)	1.13 (0.89–1.45)
Statins	23,874 (55.1)	3,792 (41.5)	1.17 (1.11–1.23)
Sulfonylureas	28,399 (65.6)	4,443 (48.6)	1.57 (1.49–1.65)
Testosterone	250 (0.6)	30 (0.3)	1.42 (0.96–2.11)
Theophyline	275 (0.6)	44 (0.5)	1.39 (1.00–1.94)
Thiazolidinediones	14,085 (32.5)	1,954 (21.4)	1.46 (1.38–1.55)

Additional Design Approaches to Reduce Unmeasured Confounding

- External control for confounding (e.g., Stürmer et al., Med Care 2007)
- Instrumental variables (e.g., Brookhart et al, Epidemiology 2006)
- Excluding patients treated contrary to prediction (in the tails of the PS distribution; Stürmer et al., AJE 2010)

Conclusions Study Design to Control for Unmeasured Confounding

- Conditioning on indication has major impact reducing potential for confounding by indication and frailty
- Can in practice only be achieved with new user, active comparator design (no nonexp. “placebo”)
- Carefully assess potential for remaining confounding by indication (clinician input)

Brief History of New User, Active Comparator Design

- Kramer et al. J Chron Dis 1987;40:1073-85:
  - ***"For what period of time?*** The risk posed by a drug for a .. event is not generally the same in the sixth month of chronic therapy as in the first or second week."
  - ***"Compared with what?*** .. it is important to compare that risk with that of some other real therapeutic option for patients with the same clinical indication. Just as in a clinical trial investigating treatment efficacy, any epidemiologic study of treatment risks should compare two or more viable treatment alternatives."
  - ".. measuring risks conditionally on .. indication is .. essential to reduce confounding"

- Guess. J Clin Epidemiol 1989;42:1179-84:
  - "The possibility of temporally non-constant hazard functions should be considered in the study design. *This requires that drug exposure time be measured not only in relation to onset of the study disease but also in relation to start of therapy with the study drug." (Italics by author)*

Brief History of New User, Active Comparator Design

- Moride, Abenhaim. J Clin Epidemiol 1994;47:731-7:
  - "Our results .. are compatible with .. a selection process by which patients who have used the drugs in the past and tolerated them well remain on the drugs while patients who are susceptible to gastropathy select themselves out of the population at risk. This process is analogous to the .. "healthy worker effect".. If not taken into account .. it could introduce a selection bias."
- Ray, Maclure, Guess, Rothman. Inception Cohorts in Pharmacoepidemiology. Symposium, 17th ICPE, Toronto 2001.
- Ray. Am J Epidemiol 2003;158:915-20:
  - "First, prevalent users are "survivors" of the early period of pharmacotherapy … Second, covariates .. often are plausibly affected by the drug itself."
  - "A new-user design eliminates these biases by restricting the analysis to persons under observation at the start of the current course of treatment"

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- Kramer, Lane, Hutchinson. Analgesic use, blood dyscrasias, and case-control pharmacoepidemiology. A critique of the International Agranulocytosis and Aplastic Anemia Study. J Chron Dis 1987;40:1073-85.
- Guess. Behavior of the exposure odds ratio in a case-control study when the hazard function is not constant over time. J Clin Epidemiol 1989;42:1179-84.
- Moride, Abenhaim. Evidence of the depletion of susceptibles effect in non-experimental pharmacoepidemiologic research. J Clin Epidemiol 1994;47:731-7.
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