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Predictors and Consequences of Severe Hypoglycemia in Adults with Diabetes

A Systematic Review of the Evidence

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Disclosure

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VA Evidence-based Synthesis (ESP) Program Overview

- Sponsored by VA Office of Research & Development, Quality Enhancement Research Initiative (QUERI).
- Established to provide timely and accurate syntheses/reviews of healthcare topics identified by VA clinicians, managers and policy-makers, as they work to improve the health and healthcare of Veterans.
- Builds on staff and expertise already in place at the Evidence-based Practice Centers (EPC) designated by AHRQ. Four of these EPCs are also ESP Centers:
  - Durham VA Medical Center; VA Greater Los Angeles Health Care System; Portland VA Medical Center; and Minneapolis VA Medical Center.

Evidence-based Synthesis Program (ESP)

- Provides evidence syntheses on important clinical practice topics relevant to Veterans, and these reports help:
    - develop clinical policies informed by evidence,
    - the implementation of effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures, and
    - guide the direction for future research to address gaps in clinical knowledge.
- Broad topic nomination process – e.g. VACO, VISNs, field – facilitated by ESP Coordinating Center (Portland) through online process:

http://www.hsrd.research.va.gov/publications/esp/TopicNomination.cfm

Evidence-based Synthesis Program (ESP)

- Steering Committee representing research and operations (PCS, OQP, ONS, and VISN) provides oversight and guides program direction.
- Technical Expert Panel (TEP)
    - Recruited for each topic to provide content expertise.
    - Guides topic development; refines the key questions.
    - Reviews data/draft report.
- External Peer Reviewers & Policy Partners
    - Reviews and comments on draft report
- Final reports posted on VA HSR&D website and disseminated widely through the VA.

http://www.hsrd.research.va.gov/publications/esp/reports.cfm

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Predictors and Consequences of Severe Hypoglycemia in Adults with Diabetes

(June 25 2012)

Full-length report available on ESP website:

http://www.hsrd.research.va.gov/publications/esp/reports.cfm

Background

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- Prevalence of Type 2 Diabetes increasing
  - Estimated at 25% in VA
- Associated with increased risk of CVD
- National guidelines have emphasized very tight glucose control
  - Prevent microvascular complications
- Tight control associated with hypoglycemia

Key Questions

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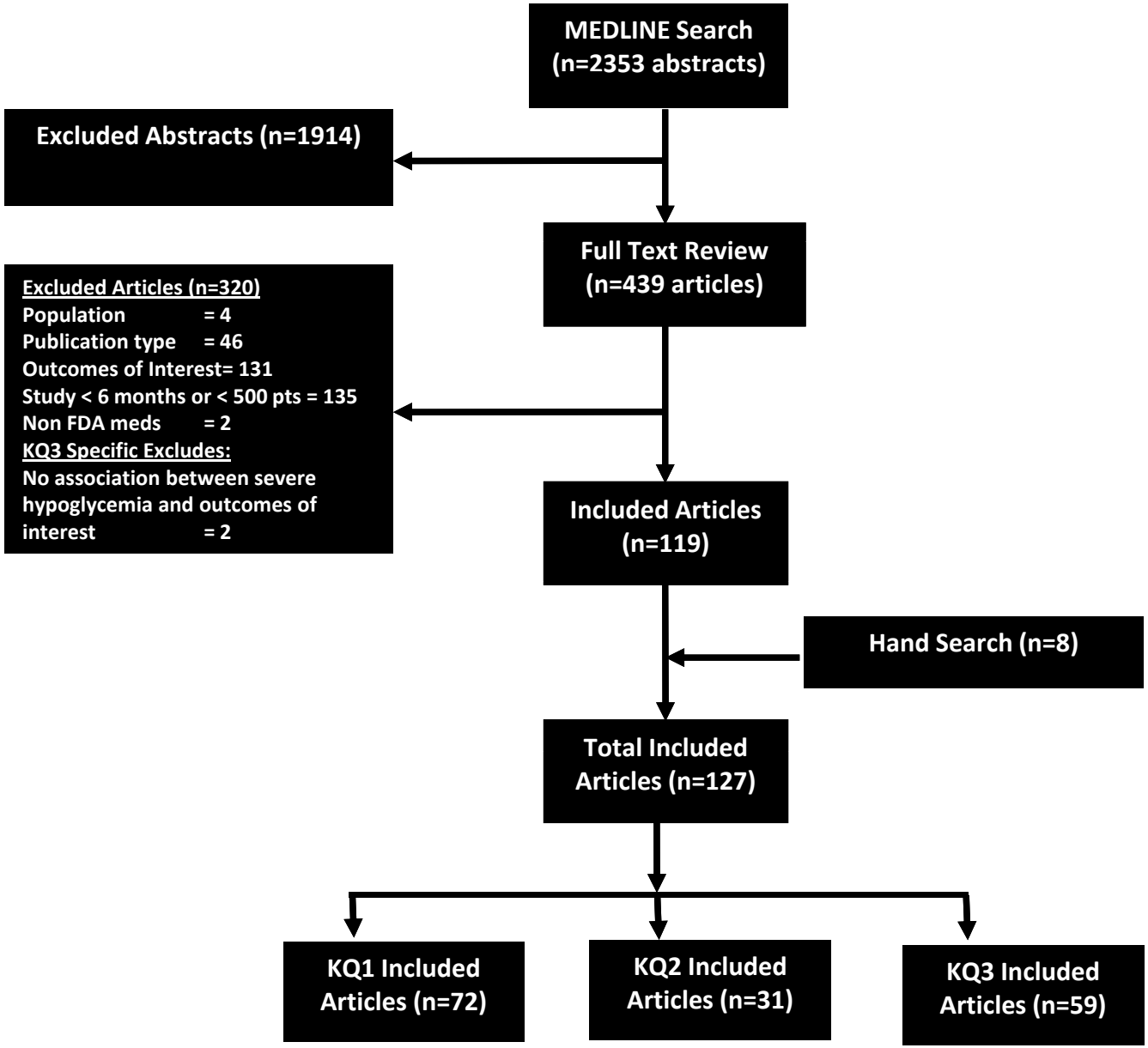
- What is the incidence of severe hypoglycemia in adults with Type 2 Diabetes on one or more hypoglycemic agents?
- What are the risk factors for severe hypoglycemia in this population?
- What are the consequences of severe hypoglycemia?

Methods

- Medline search for trials, observational studies and systematic reviews (1950 to November 2011) of adults with type 2 diabetes on diabetes medication
- Severe hypoglycemia defined as an episode with typical symptoms resolving after treatment (IV glucose, IM glucagon or PO carbohydrate) administered by another person
- For KQ1 and 2, studies with < 500 subjects or < 6 months duration were excluded

Literature Search



KQ1: Incidence

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- 60 studies (72 articles)
  - most were RCTS (46) & funded by drug companies (47)
  - 5 intensive vs. standard control
- Only 12/46 RCTS were rated as good quality
- Severe hypoglycemia seen infrequently in studies of
  - Metformin, Glinides, Detemir
  - TZDs, GLP-1 Analogs
  - DPP-4 inhibitors

KQ1: Incidence

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- Highest rates for…
- Insulins
  - NPH monotherapy 9.3% over 3.5 yrs* (95% CI 7.3 to 11.8, N=763, 2 studies)
  - Glargine
    - > 2 years: 4.1% (95% CI 1.9 to 8.4%, N=1223, 3 studies)
    - < 1 yr: 1.6% (95% CI 1.6%, 95% 0.8 to 3.2%, N=13,088, 5 studies)
  - Lispro 3.6% over 1.3 yrs* (95% CI 2.3 to 5.4,N=1198, 2 studies)
  - Glulisine + NPH 1.0% over 0.5 years* (95% CI 0.5 to 2.1%, N=883, 2 studies)
- Sulfonylureas 1.2% over 2.3 yrs* (95% CI 0.9 to 1.4, N=9081,13 studies)

** weighted mean average duration*

KQ1: Intensive Control

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Study	Standard	Intensive	Average Follow-up (Years)	Definition	Glycemic Targets (standard /intense)
ACCORD[3]	261/5123 (5.1%)	830/5128 (16.2%)	3.5	HA	A1c 7.0 – 7.9 A1c < 6.0
ADVANCE[4]	81/5569 (1.5%)	150/5571 (2.7%)	5.0	HA	Local standards A1c ≤ 6.5
VA-DT[5]	28/899 (3.1%)	76/892 (8.5%)	5.6	**	A1c < 9 A1c < 6
VA-CSDM[30]	2/78 (2.6%)	5/75 (6.6%)	2.3	HA	A1c < 13 A1c 4.0 – 6.1
UKPDS[#21, 29]	8/1138 (0.7%)	33/3071 (1.1%)	10.0	HA	FPG 6.1 – 15.0 mmol/l FPG < 6.0 mmol/l
POOLED	**3.1%**	**7.6%**	**5.2 yrs**	**RR 2.4** (95% CI 1.8 to 3.1, N=27,644)	

***** life threatening or resulted in death, hospitalization, disability or incapacity*, *# data for the 2 UKPDS studies are combined as per Hemmingsen 2011*, *HA—episode of hypoglycemia requiring assistance of another person***

KQ1: Population-Based

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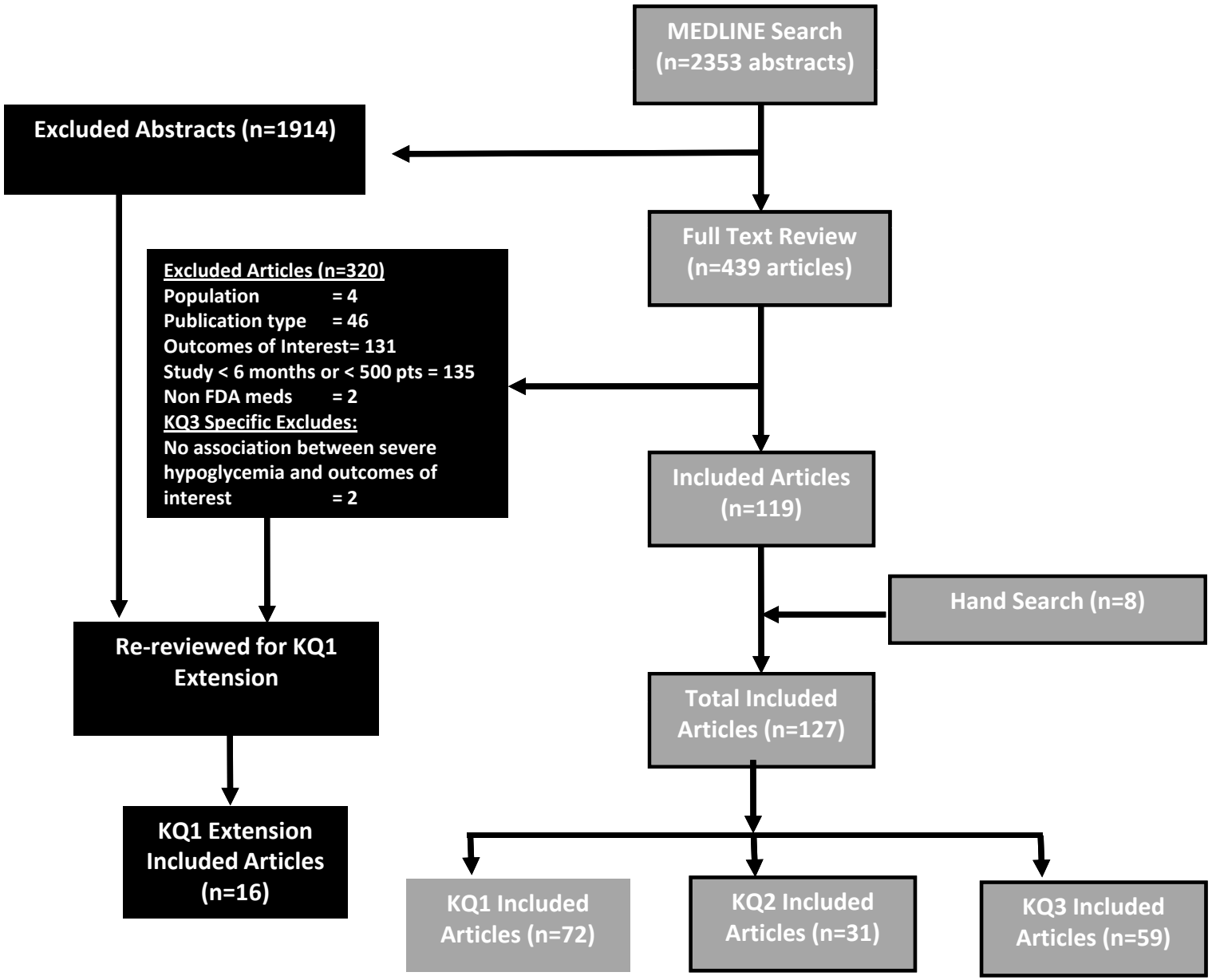
- **In order to gain a more population-based perspective on hypoglycemia incidence**
- **We re-reviewed all the abstracts to find articles with data from more representative groups…**
  - Population or clinic based (no drug RCTs)
- **…using more liberal inclusion criteria**
  - <500 people, duration < 6 months
  - Definition of severe hypoglycemia not as rigorous
  - Lack of true incidence data (cross sectional surveys)

Literature Search



KQ1: Incidence

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- 13 survey studies (patient recall)
  - 5 six month studies in pts on oral agents only
    - 1-13% incidence hypoglycemia requiring any assistance (HA)
    - 1-4% incidence hypoglycemia requiring medical assistance (HMA)
  - 3 one year studies in pts on insulin only
    - 12-17% HA
    - 2% HMA
- 1 prospective study
  - 1 month community based in Scotland
  - 173 adults
  - 3% incidence of HA

KQ1: VA Specific Data

- Four of our included studies were of VA patients
- 2 additional VA studies did not meet our inclusion criteria or were published later
- These studies suggest that VA patients may experience higher incidence rates than the general population

KQ1: Limitations

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- **Data mostly from drug company sponsored trials**
  - **highly selected pts**
  - **ascertainment bias**
- **Population based data**
  - **patient recall**
  - **lack of standard definitions**

KQ1: Summary

- Incidence of severe hypoglycemia: 0-3%/yr
- Highest for
  - Insulins
  - Sulfonylureas
  - Regimens targeting tight control
- Prospective population based studies needed
  - VA and non-VA

KQ2

- What are the risk factors for severe hypoglycemia in adults with Type 2 diabetes on one or more hypoglycemic agents?

KQ2: Risk Factors for Hypoglycemia

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- 28 studies (31 articles)
- Only the 12 studies that used multivariate analysis are reported
  - 2 RCTs
  - 2 cohort
  - 4 cross-sectional
  - 4 case control

KQ2: Risk Factors for Hypoglycemia

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- Transient causes (e.g. missed meal, excess exercise, alcohol use, acute infection) were not included

- All studies met pre-specified definition of severe hypoglycemia

- Data were unsuitable for pooling
  - lengths of f/u
  - risk factors
  - populations

KQ2: Independent Risk Factors Consistently Associated with Risk of Hypoglycemia

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- Demographics
  - lower education level
  - African American race
- Medical History
  - past hypoglycemia
  - renal insufficiency
  - non-renal microvascular complications
  - dementia
  - longer diabetes duration
- Treatment
  - intensive diabetes control

KQ2: Independent Risk Factors NOT Consistently Associated with Risk of Hypoglycemia

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- Gender, Age and BMI
  - In the two largest studies, higher age and lower BMI were significantly associated with higher risk

KQ2: Inadequately Studied Risk Factors

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- h/o hypoglycemia unawareness
- genetic markers
- marital status
- smoking
- alcohol consumption
- polypharmacy
- recent discharge from the hospital
- congestive heart failure
- use of ACE inhibitors

KQ2: Limitations and Summary

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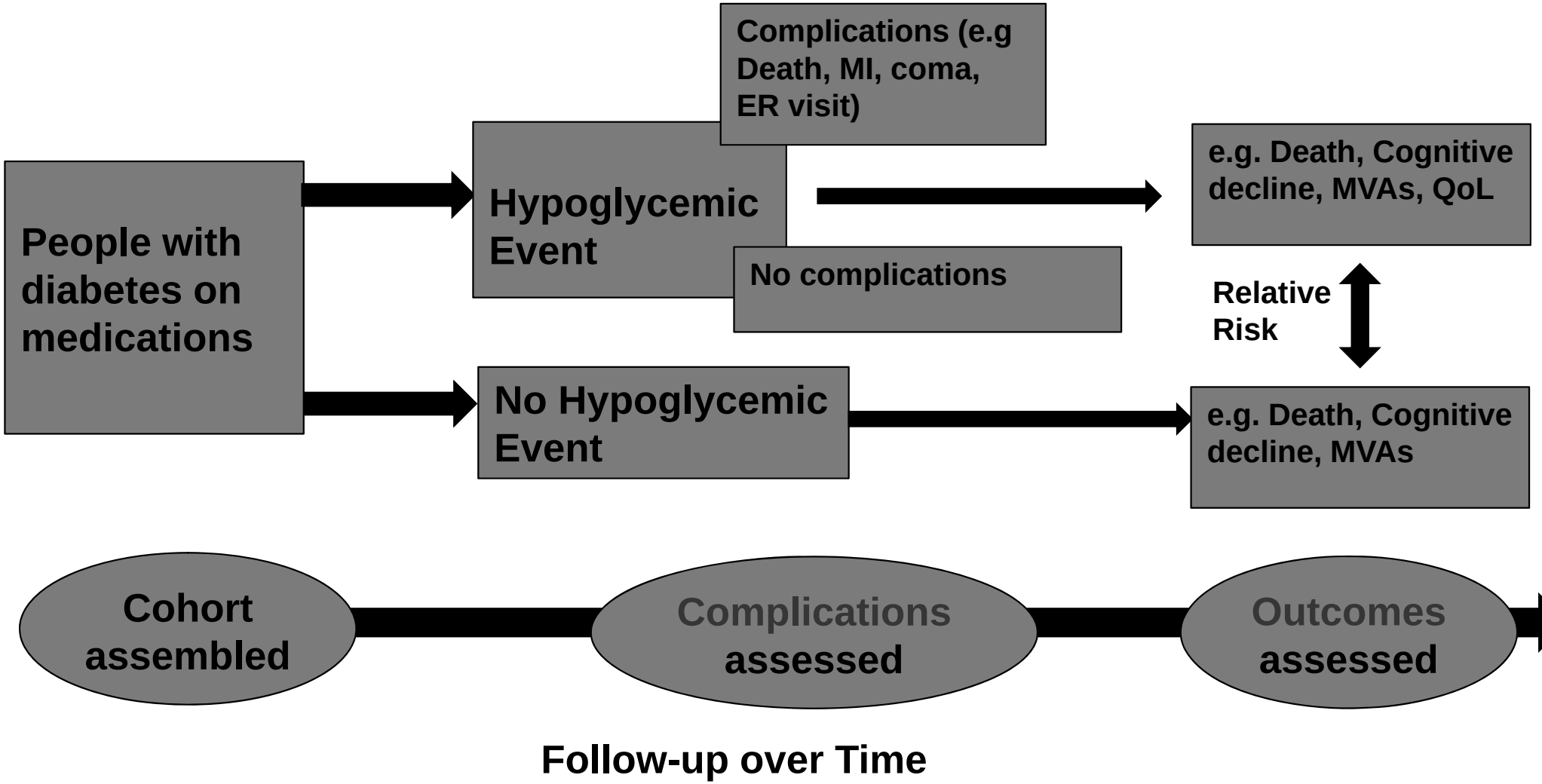
- Publication Bias
  - Negative studies unlikely to be reported
- Risk Factors
  - lower education level
  - African American race
  - past hypoglycemia
  - renal insufficiency
  - non-renal microvascular complications
  - dementia
  - longer diabetes duration
  - intensive diabetes control
  - ?higher age
  - ?lower BMI

KQ3

- What are the consequences of severe hypoglycemia?

KQ3: Ideal Study Design



Features of an Ideal Study

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- Population based
- Prospective
- Controlled
  - People with diabetes on medications who did NOT have hypoglycemia
- *Most studies were far from this ideal*

KQ3: Consequences of Hypoglycemia

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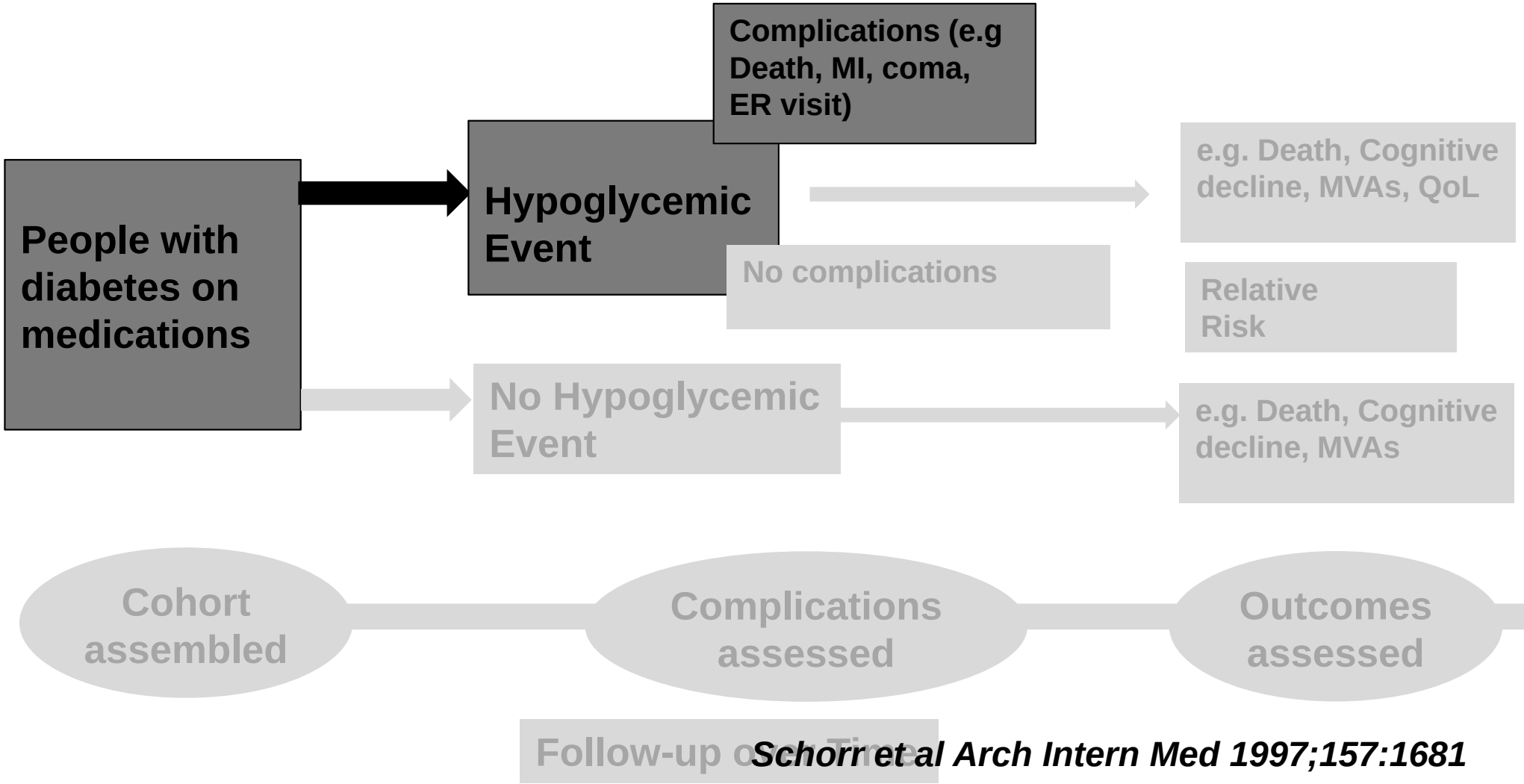
- 59 articles on 53 studies
- Consequences
  - Complications at Presentation
  - Long-Term Outcomes
    - All-cause mortality
    - Cognitive Impairment
    - Quality of Life

Complications at Presentation

- Retrospective cohort study of 19,932 Tenessee medicaid enrollees, age ≥65, on oral hypoglycemics or insulin
  - ✓ Population-based
  - +/- Prospective
  - ✗ Control Group

Schorr et al Arch Intern Med 1997;157:1681

Study Design



Schorr et al Arch Intern Med 1997;157:1681

Complications at Presentation

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- 586 persons with a first episode of serious hypoglycemia occurring outside the hospital that resulted in an ER visit, hospitalization or death
- 5% of these episodes were associated with 'catastrophic complications' including
  - Stroke (1.2%) or TIA (0.6%)
  - MI (0.5%)
  - Injury (1.7%)
  - Death (0.3%

Schorr et al Arch Intern Med 1997;157:1681

Long Term Outcomes: Mortality

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ACCORD and ADVANCE

+/- Population-based

- RCTs, but liberal entrance criteria

✔Prospective

- With long follow-up

✔Control Group

- With no episodes of hypoglycemia

Mortality

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- Severe hypoglycemia was associated with an increased risk of death in both ACCORD and ADVANCE

Mortality

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in people <u>without</u> a h/o severe hypoglycemia

Study	Mortality			
	Intensive		Standard	
Hypoglycemia	Yes	No	Yes	No
ACCORD (annual)	2.8%	1.2%	3.7%	1.0%
ADVANCE (annual)	3.6%	1.8%	5.1%	1.9%
UKPDS (10 yr)	12.5%	NR	0%	NR

Mortality

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in people <u>with</u> a h/o severe hypoglycemia

Study	Mortality			
	Intensive		Standard	
Hypoglycemia	Yes	No	Yes	No
ACCORD (annual)	2.8%	1.2%	3.7%	1.0%
ADVANCE (annual)	3.6%	1.8%	5.1%	1.9%
UKPDS (10 yr)	12.5%	NR	0%	NR

Long term Outcomes: Cognitive Impairment

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- 2 high quality cohort studies (Whitmer 2009, Bruce 2009)
  - Population-based (both)
  - Prospective (Bruce)
  - Control Group (both)
- However *Bruce 2009* was grossly underpowered
  - N=205 followed for < 2 years

Cognitive Impairment

Whitmer

- 16,667 pts with diabetes from a healthcare plan in California
- 3.8 years of follow-up for incident dementia (retrospective cohort)
- 1465 (8.8%) with one or more episodes of hypoglycemia identified retrospectively
- **Increased risk of dementia in those with 1 or more episodes (HR 1.68, 95% CI 1.47 to 1.93)**

JAMA 2009;301:1565

Long term Outcomes: Quality of Life

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- 8 cross-sectional studies
  - 5 had 1/3 quality indicators*
  - 2 had 2/3 quality indicators
  - 1 had 0/3

**Population based, prospective, control group*

Quality of Life

Study	Quality Indicators	HRQoL	Worry/ Fear	Other
Marrett, USA, 2009	2/3	↓	↑	
Labad, Scotland, 2010	2/3	-	-	Increased anxiety
Petterson, Sweden, 2011	1/3	↓	↑	
Hermanns, Germany, 2005	1/3	-	-	Increased anxiety & depression
Alvarez, Europe, 2010	1/3	↓	-	
Vexiau, France, 2008	1/3	↓	↑	
Davis, UK, 2005	1/3	-	-	Decreased productivity

In diabetics reporting severe hypoglycemia compared to those reporting no severe hypoglycemia

All results are significant at $p<0.05$

Accidents / Trauma

- No high quality studies
- ACCORD
  - No difference in # of MVAs in which pt was a driver between intense and standard control

KQ3 Summary

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- There is evidence that severe hypoglycemia
  - Decreases quality of life
  - Is associated with increased mortality
  - May lead to cognitive impairment
  - Increases hospital and ER utilization (data not shown)
- Limitations
  - Few high quality studies (population based, prospective, control group)

Conclusions

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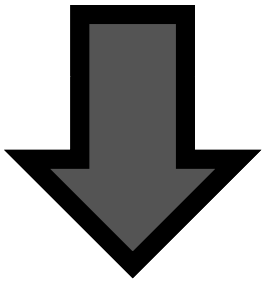
In patients with diabetes on medications…

- Incidence of severe hypoglycemia is difficult to quantify but is not negligible
- Several co-morbidities, demographic and treatment related factors increase the risk
- Severe hypoglycemia has a negative effect on QoL and can lead to serious outcomes including death
- Intensity of glucose control is the risk factor most amenable to intervention

National Recommendations

Goal A1C: "< 7% in most patients"

ADA Standards of Medical Care (2011)



Patient centered approach

Less stringent goal (7.5 to 8.0) appropriate for some

ADA and EASD (2012)

Patient-centered Approach

ADA and EASD (2012)

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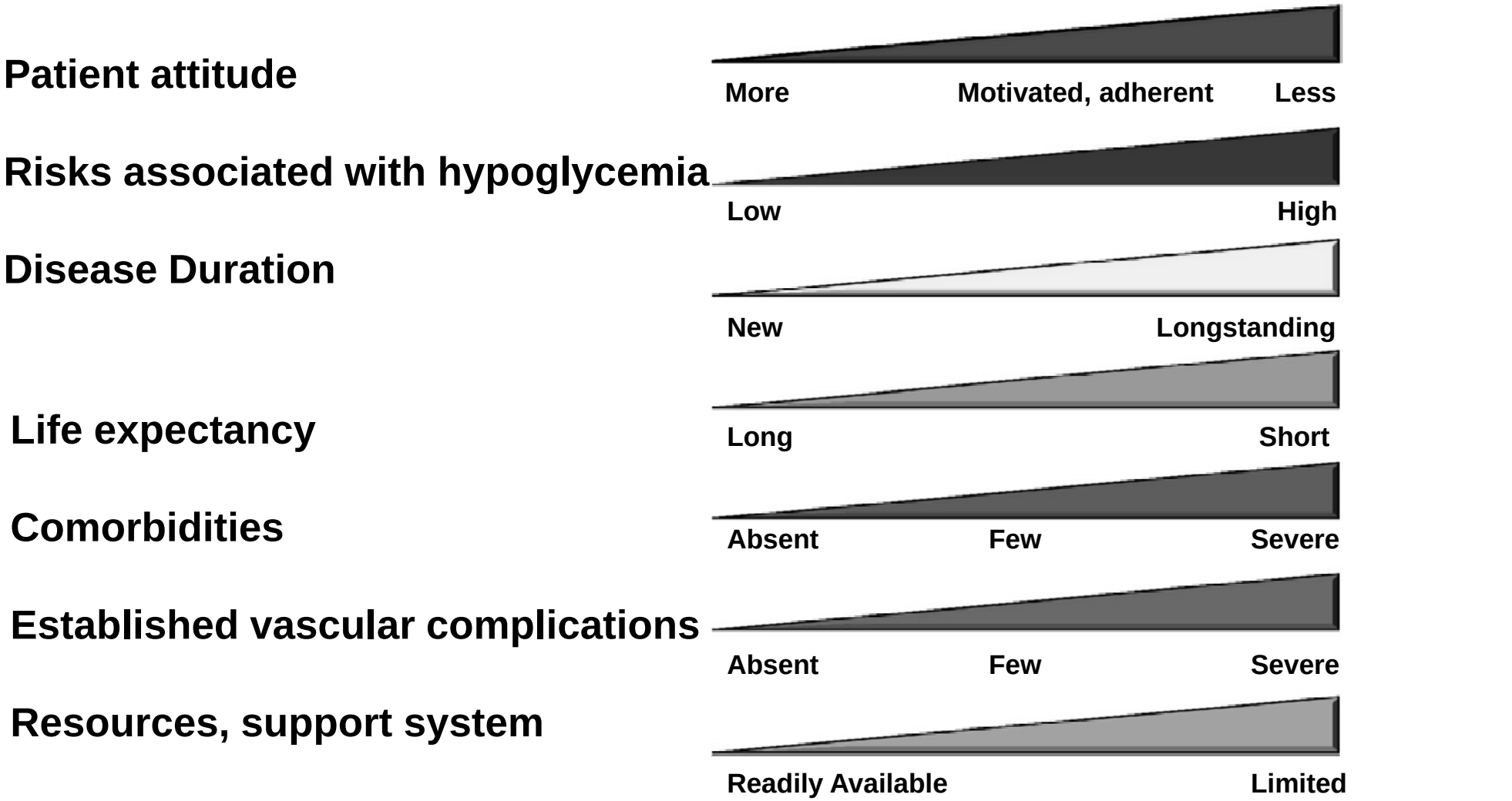
Glycemic Control **More stringent** **Less stringent**



VA-DoD Guidelines 2010

- Individualized goal based on…
  - Co-morbidities
  - Life expectancy
  - Risk of hypoglycemia
  - Presence of pre-existing microvascular complications
  - Patient's preferences

VA-DoD Guidelines 2010

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Goal A1C

Microvascular complications

Life Expectancy	Absent or Mild	Moderate	Advanced
> 10 years	<7%	<8%	8-9%
5-10 years	< 8%	<8%	8-9%
< 5 years	8-9%	8-9%	8-9%

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Questions?

If you have further questions,
feel free to contact:

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The full report and cyberseminar presentation is available on the ESP website:

http://www.hsrd.research.va.gov/publications/esp/

Key Summary Points Regarding Potential Risk of Hypoglycemia in Veterans

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National Program Director Endocrinology and Diabetes

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Chair Medication Advisory Panel

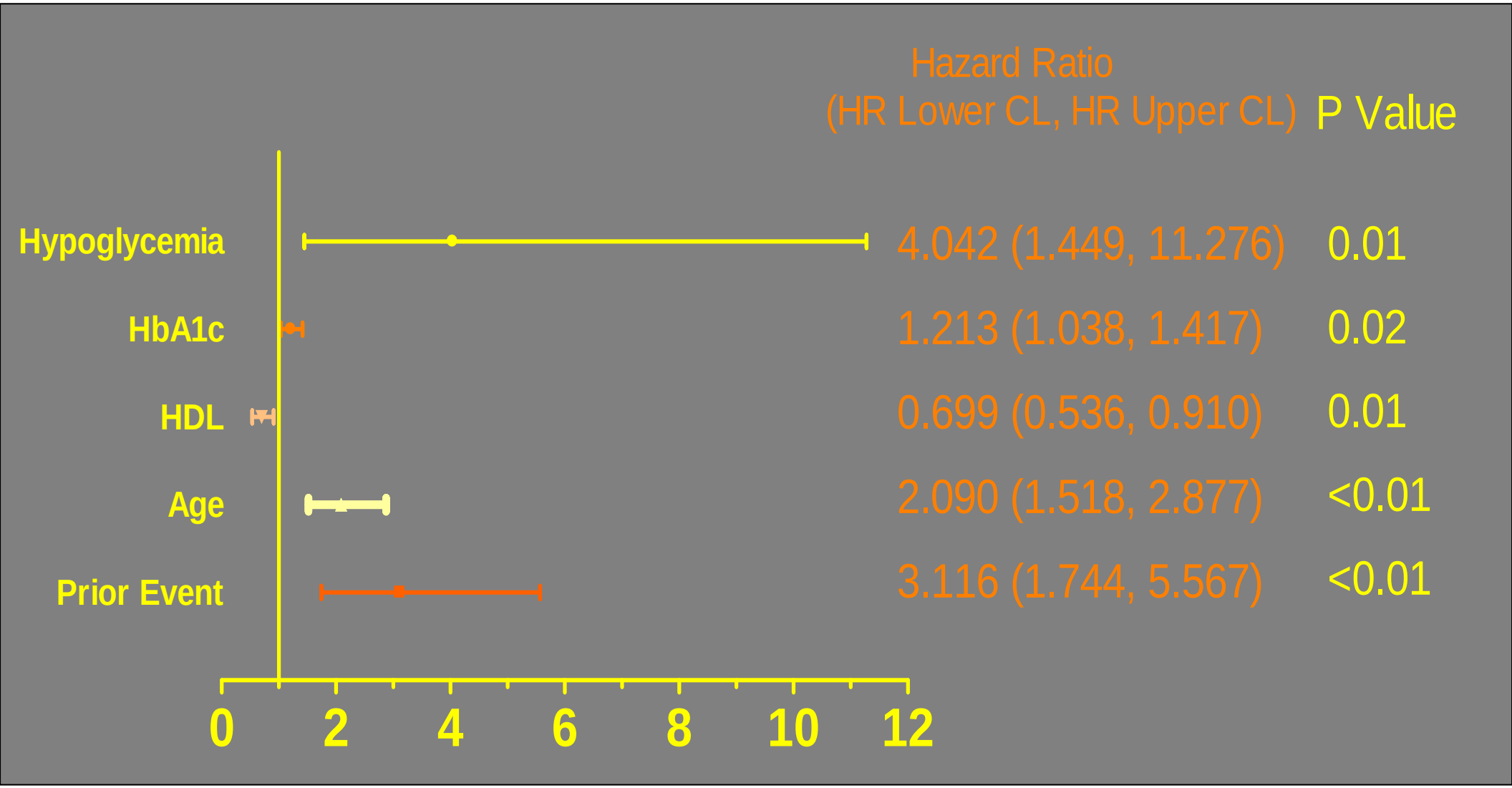
ACCORD

- Increased mortality (2.8%) in intensively managed patients who had one or more severe hypoglycemic episodes compared to those with no episodes (1.2%) (adjusted HR 1.41; 95% CI, 1.03-1.93).
- Trend was also seen in the standard control group: 3.7% vs. 1.0%, respectively (adjusted HR 2.3; 95% CI, 1.46-3.6).

ADVANCE

- Severe hypoglycemia was associated with a significant increase in the adjusted risks of major macrovascular events (hazard ratio, 2.88; 95% confidence interval [CI], 2.01 to 4.12), major microvascular events (hazard ratio, 1.81; 95% CI, 1.19 to 2.74), death from a cardiovascular cause (hazard ratio, 2.68; 95% CI, 1.72 to 4.19), and death from any cause (hazard ratio, 2.69; 95% CI, 1.97 to 3.67) ($P<0.001$ for all comparisons).
- Similar associations were apparent for a range of nonvascular outcomes, including respiratory, digestive, and skin conditions ($P<0.01$ for all comparisons

Predictors of CV Death, VADT
Davis, S. ADA 2009



Risk of Morbidity and Mortality from Severe Hypoglycemia from ACCORD, ADVANCE , VADT

- Association with adverse outcomes greatest with control arms (A1cs achieved 7.5, 7.0, 8.4.% respectively.
- Risk greater in subjects with chronic co-morbid conditions
- Unlikely that post-hoc observational data sets will disentangle relationship of hypoglycemia to outcomes

Risk Factors for Serious Hypoglycemia Among Veterans Under-Represented in Trials

- 2004 Risk Factors <65 years (Pogach et al. Diabetes Care 2010)
  - Complex Glycemic Regimens 30%
  - Decreased Life Expectancy, 5.4%
  - Advanced Complications 6.3%
  - Serious Medical Conditions 9.0%
  - Serious Neurological Conditions 4.2%
  - Serious Mental Health Conditions 21.5%
  - Poverty 28%; disability >50% 31.3%

Conclusions:

- The Veteran population is at high risk for serious hypoglycemia due to age, risk factors (medical, socio-economic)
- Incidence/Prevalence of serious hypoglycemia not likely to be known with greater certainty without weighted population health surveys.
- Clinicians need to balance benefits of good glycemic control with potential harms associated with hypoglycemia, especially in vulnerable veterans
- PBM will address issue of anti-glycemic safety among those high risk Veterans in near future.