Background Material

August 30, 2006

Medicare Coverage Advisory Committee
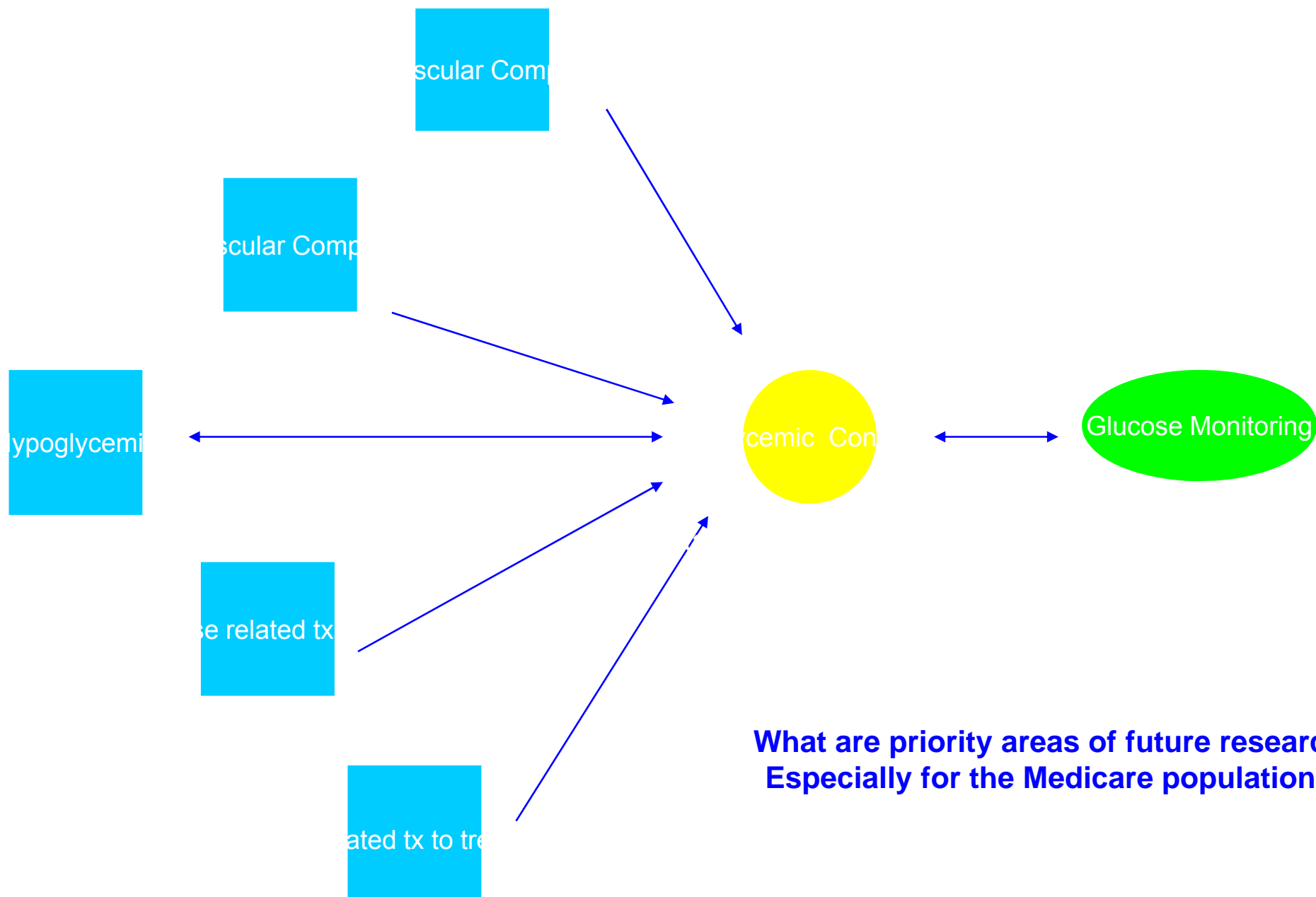
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Topic

Relationship between:

- **glycemic control (HbA1c) & chronic diabetic complications (*especially cardiovascular*)**

- **glycemic control (HbA1c) & frequency of chronic outpatient glucose monitoring**

- **the frequency of glucose monitoring & chronic complications**

Particularly for Type 2 diabetic patients $\geq$65

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Defining areas of current knowledge

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Glucose Monitoring

**What are priority areas of future research?
Especially for the Medicare population?**

Goals

- **Explore what is known**

- **Identify gaps in our knowledge**

- **Identify relevant areas of ongoing research**

- **Delineate areas for future research**

WHY?

- **Evolution in glucose monitoring**

- **Emerging data: DCCT paradigm ? not relevant to older Type 1 patients or to Type 2 patients**

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Glucose Monitoring Evolution

Urine Test Strips

- Temporally delayed from plasma measurements

- Affected by renal threshold that changes with age

Visual Blood Test Strips

- Requires timing

- Requires ability to match colors

Initial Blood Glucose Meters

- Bulky

- Requires timing

- Requires relatively large amounts of blood

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Glucose Monitoring Evolution

Later Blood Glucose Meters

- More expensive strips; cannot cut in ½; cost $0.25-1.00/strip

Interstitial Fluid Glucose Monitor (Continuous, now real-time data)

- Requires expensive meter (~$3000) & sensors (~$50 q3 days)

- Requires calibration with blood glucose test strips

- Accuracy issues (psuedohypoglycemia; different results on different sides of body; Fiallo-Scharer 2005, Larsen 2004)

Meters Extracting Interstitial Fluid via Transdermal Electro-osmosis (Continuous, now real-time warning data)

- Requires expensive meter (~$875) and sensors (~$14/day)

- Requires calibration with blood glucose strips

- Can be dislodged, affected by temperature or perspiration

- Can cause skin irritation

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Diabetes Population Features

	Type 1	Type 2
Relative Proportion	~10%	~90%
Peak Incidence	Teens	50-70 yrs

(Medicare population even more skewed to older type 2 diabetic patients)

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Diabetes Disease Features

Type 1

- **Auto-immune--may have other antibody mediated diseases**

- **Progressive islet cell destruction>affects insulin & perhaps glucagon**

- **Insulin absence is KEY**

- **May have residual function>better prognosis**

- **Disease-related hypertension occurs only after onset of renal disease**

Type 2

- **Polygenic**

- **Weight gain & medications can exacerbate; reversibility**

- **Insulin resistance is KEY; insulin reserve may be impaired, but not absent**

- **Hypertension & lipid problems often present before hyperglycemia**

- **Hyperglycemia may be disease marker rather than a central pathogenic feature**

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Diabetes Complications

Type 1

- **Acute:**
  Hypoglycemia
  Ketoacidosis

- **Chronic:**
  Microvascular
      Retinopathy
  (< risk with older age onset-Kullberg 2002)
      Nephropathy (former killer)
  (decrease since 1965; peak after 15-20 yrs-then plateau-Finne 2005)

  Macrovascular

      Cardiovascular
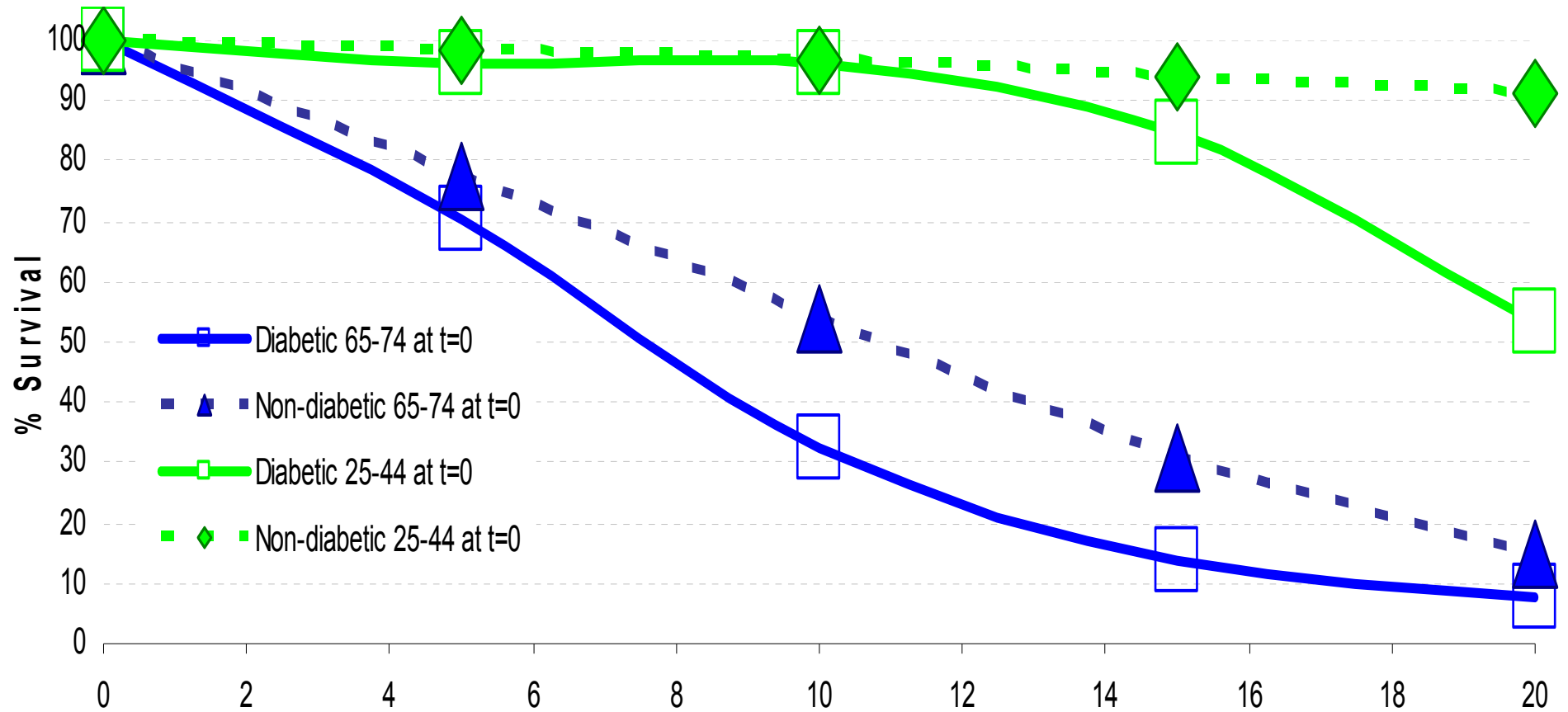   **(long-term survivors; renal link)**

Type 2

- **Acute:**

  Hypoglycemia
    (1/10-1/100 as likely in Type 1; Risk not equal in Rx classes; Risk much higher in infirm pts)
  (Holstein 2003, Murata 2005)
  Hyperosmolar coma (rare)

- **Chronic:**

  Microvascular
      Retinopathy
      Nephropathy
   Macrovascular
      CARDIOVASCULAR

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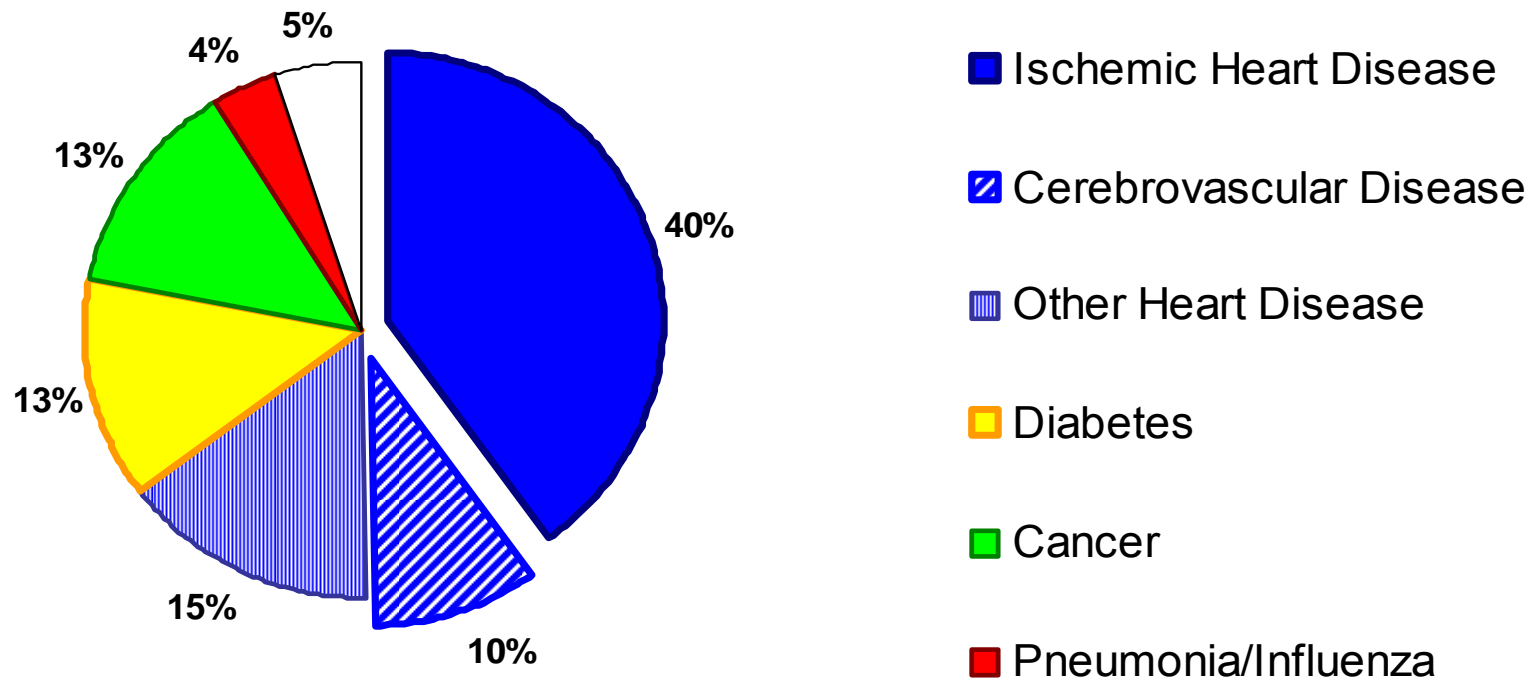
Life Expectancy Reduction in Diabetic Compared to Non-diabetic Subjects (Yrs)

Age*	Marks/Krall	Goodkin	Panzram/Zabel
10-14	17	27**	
15-19	~16.5	23	
20-29	~13	16	
30-39	~10.5	11	
40-49	~8.5	10	~7.5
50-59	~6.5	6	~5.5
60-69	~4.5	5***	~3.5
≥70			3

**Percent Survival during Follow-up
NHANES I Cohort from 1971-5 (Men)**

% Survival

- Diabetic 65-74 at t=0
- Non-diabetic 65-74 at t=0
- Diabetic 25-44 at t=0
- Non-diabetic 25-44 at t=0

Cause of Death in Diabetes
(Death Certificates)

Legend:
- Ischemic Heart Disease
- Cerebrovascular Disease
- Other Heart Disease
- Diabetes
- Cancer
- Pneumonia/Influenza

Pie chart values: 40%, 10%, 15%, 13%, 13%, 4%, 5%

DCCT (Diabetes Control & Complications Trial)

Type 1 (aged 13-39) **(t_0=Glycosylated Hb 8.8-9.0%)**

N=726 Primary (1°) prevention

    No baseline retinopathy

    Urine albumin <40 mg/d

N=715 Secondary (2°) Prevention

    Mild to moderate proliferative retinopathy

    Urine albumin <200 mg/d

Tx: 2 shots vs $\geq$3 shots or pump w adjustments

Follow-up 6.5 yrs. Glycated Hb difference ~2% units

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DCCT Results (1993)

- **Validated use of glycated hemoglobin as a surrogate marker for stepped retinopathic risk in young Type 1 patients using insulin**

- **Blindness & renal failure not endpoints**

- **Intensive treatment slowed progression, but did not reverse pre-existing disease**

- **Tx did not alter cardiovascular outcomes**

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DCCT: Event Rates/100 Patient-Years

	1º Int	1º Conv	P	2º Int	2º Conv	P
≥3step Retinopathy Δ	4.7	1.2	SS	7.8	3.7	SS
Macular Edema	--	--	ns	3.0	2.0	ns
Severe Retinopathy	--	--	ns	2.4	1.1	SS
Laser Tx	--	--	ns	2.3	0.9	SS
New Urine-albumin ≥40 mg/d	3.4	2.2	SS	5.7	3.6	SS
New Urine-albumin ≥300 mg/d (Fewer if +ClCr <70)	0.3	0.2	ns	1.4	0.6	SS
New Clinical Neuropathy	9.8	3.1	SS	16.1	7.0	SS
CVD	--	--	ns	--	--	ns

DCCT: Retinopathy vs Glycated Hb

Relationship of retinopathy progression (3 steps) & glycemic control > NOT LINEAR

Glycated Hb (%)	Retinopathy Progression/100 Pt-Yrs
10.5	~10
7.5	~2.8
5.5	~0.8

DCCT: Retinopathy vs Δ in Glycated Hb

Relationship of retinopathy progression & glycemic control >NOT LINEAR < benefit per unit Δ in glycated hb at low glycated hb levels than high glycated hb levels

Interval Δ in Glycated Hb (%)	Δ in Retinopathy Progression/ 100 Pt -Yrs
10.5 to 9.5	~2.9
9.5 to 8.5	~2.4
8.5 to 7.5	~1.8
7.5 to 6.5	~1.0
6.5 to 5.5	~1.0

DCCT: Hypoglycemia vs Glycated Hb

**Relationship of severe hypoglycemia & glycemic control >
NOT LINEAR**

Glycated Hb (%)	Severe Hypoglycemic Events/100 Pt-Yrs
10.5	~28
7.5	~57
5.5	~105

DCCT: Retinopathy vs Δ in Glycated Hb

**Relationship of hypoglycemia & glycemic control
>NOT LINEAR**

>events/unit Δ glycated hb at low than high levels

Interval Δ in Glycated Hb (%)	Δ in Severe Hypoglycemic Events/ 100 Pt -Yrs
10.5 to 9.5	**~3**
9.5 to 8.5	**~11**
8.5 to 7.5	**~15**
7.5 to 6.5	**~16**
6.5 to 5.5	**~32**

DCCT: Cardiovascular Disease

- **Cardiovascular (including peripheral vascular) events uncommon even when 1º & 2º cohorts combined**

- **Intensive Tx: 0.5 events/100 patient-yrs**

- **Conventional Tx: 0.8 events/100 patient-yrs**

$\Rightarrow$ **Absence of treatment effect attributed to**

YOUNG PATIENT AGE

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UKPDS (UK Prospective Diabetes Study)

Type 2 (aged 25-65) (t_0=HbA1c 7.05 & 7.09 %)

N=3867 newly diagnosed

Exclusion of creatinine >175 umol/l, recent MI, >1 vascular event, prior laser surgery

Intensive tx target: Fasting glucose <108 mg/dl

Non-obese>insulin vs SU Obese>metformin

Conventional: Add drugs if fasting >270 mg/dl or sx

Diet>insulin vs SU

Follow-up: ~10 yrs.   HbA1c difference ~0.9% units

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UKPDS Endpoints: Composite

Diabetes-related endpoint

- CV: Angina, CHF, MI, stroke
- EYE: Blindness ($\leq$6/60) , cataract extraction, photo-coagulation, retinal hemorrhage
- KIDNEY: Renal failure (dialysis or creatinine >250 umol/L
- MISC: Amputation
- DEATH: MI, metabolic (hyper, hypoglycemia), sudden death

Diabetes-related death

- MI, metabolic (hyper, hypoglycemia), peripheral vascular disease, renal disease, sudden death

All cause mortality

Hypoglycemia (not aggregate)

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UKPDS Endpoints: Surrogate

CV:

- Minnesota coding of cardiac ischemia
- LVH (ratio $\geq$0.5)
- Peripheral pulses decrease
- ankle-brachial indices decrease

EYE:

- 3 line Δ in ETDRS
- Inability to drive car ($\geq$0.3 logMAR)
- US legal blindness ($\geq$0.7 logMAR)
- WHO blindness ($\geq$1 logMAR)
- Microaneurysm ($\geq$1)
- 2 step retinopathy Δ

KIDNEY:

- Microalbuminuria (>50 mg/L-preservation issues)
- Proteinuria (>300 mg/L
- >2x Δ in creatinine

NEUROPATHY:

- Impaired bioesthesiometer sensation
- Impaired RR interval
- Impotence
- Orthostatic hypotension
- Reflex (knee, ankle) loss

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UKPDS Results (1998)

- **Study powered to detect 40% change. Not present after 10 study years (1987) so repowered for detection of 15% change & more patients added.**

- **Risk reduction for 1° aggregate microvascular events: 25% (p=0.01).**

  ⇒ **Primarily due to <photocoagulation**

  ⇒ **Visual acuity (surrogate) not better**

  ⇒ **Few patients developed renal failure or died from ESRD**

  ⇒ **Microalbuminuria prevalence > with duration, but not proteinuria & serum creatinine (all surrogates)**

  ⇒ **Neuropathy parameters including impotence (surrogates) except bioesthesiometer sensitivity at 15 years not better**

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UKPDS Results

- **Tx did not alter cardiovascular outcomes despite population 18 yrs older than DCCT. (Only p=0.052 for MI component group.)**

- **Median complication-free interval (most frequently eye-related) was 14 years in the intensive group & 12.7 years in the conventional group (p=0.029); Time to first complication delayed for 15 months.**

- **Treatment of 19.6 patients x 10 years to prevent any single endpoint complication in 1 patient.**

- **No clear evidence for reversal of pre-existing disease.**

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UKPDS Results

- **HbA1c validated as a surrogate marker for microvascular disease risk in middle-aged Type 2 patients, but < robust than for Type 1 patients.**

- **Generally, no major differences between the tx modalities: insulin, metformin, & sulfonylureas.**

- **Over time, HbA1c & weight $\uparrow$ in both groups. Hypoglycemia $\downarrow$.**

- **Relationship between HbA1c & microvascular disease not easily expressed as a line or curve.**

- **Relationship between HbA1c & severe hypoglycemia & not easily expressed as a line or curve.**

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UKPDS: Hypoglycemia

	% Pts w Severe Events/ Yr over 10 Yrs	Severe Events/ 100 Pt-Yr over 10 yrs	Median HbA1c over 10 Yrs	Median HbA1c at 10 Yrs.
Conventional	NI	0.7	7.9%	~8.2%
Intensive-All (See subgroups)	NI	NI	7.0%	~7.9%
Insulin	2.3	1.8	7.1%	~7.9%
Chlorpropamide	0.4	1.0	6.7%	~7.8%
Glyburide	0.6	1.4	7.2%	~8.0%
Diet	0.1	NI-rare	NI	NI

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Do we have data on complication risk & impact of intervention in older patients with Type 2 diabetes?

No good direct data

$\Rightarrow$**Some modeling data by Vijan et al. 1997**

Assumptions:
  DCCT rates for incidence of early disease (? Over estimate. Kullberg 2002)
  Cohort rates for progression of disease
  Mortality factor adjusted for presence of diabetes +/- urinary albumin>CVD

Definitions:
  Blindness=20/200 or worse
  Microalbuminuria=30-300 mg/g creatinine
  Proteinuria= >300 mg/g creatinine
  ESRD=Requires dialysis or transplantation

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Life-time Risk for Blindness 2° to Diabetic Retinopathy (%)

HbA1c (%)	Age of	Diabetes	Onset	
	45 Yrs	55 Yrs	65 Yrs	75 Yrs
7	0.3	0.1	<0.1	<0.1
8	1.1	0.5	0.2	<0.1
9	2.6	1.2	0.5	0.1
10	5.0	2.5	1	0.3
11	7.9	4.4	1.9	0.5

Life-time Risk for End-Stage Renal Disease (%)

HbA1c (%)	Age of	Diabetes	Onset	
	45 Yrs	55 Yrs	65 Yrs	75 Yrs
7	2.0	0.9	0.3	0.1
8	2.7	1.3	0.5	0.1
9	3.5	1.6	0.6	0.1
10	4.3	2.1	0.8	0.2
11	5.0	2.5	0.9	0.2

Marginal Duration of Treatment to Prevent 1 Year of Blindness if Intervention Decreases HbA1c by 2% (Patient-years)

84% of benefit achieved by treating 17% of patients

HbA1c (%)	Age of	Diabetes	Onset	
	45 Yrs	55 Yrs	65 Yrs	75 Yrs
9	223	418	1135	5062
10	108	171	390	1012
11	50	113	136	816
12	28	40	61	230

Vijan, S. et. al. Ann Intern Med 1997;127:788-795

Modeling Conclusions

- **Most benefit achieved by treating youngest patients-especially those with poorest glycemic control**

- **Modest glycemic control (HbA1c 8-9%) prevents microvascular (retinal & renal) complications in older patients with Type 2 diabetes**

Veterans Affairs Cooperative Study on Glycemic Control & Complications in Type 2 Diabetes (VA CSDM)

Type 2 (aged 40-69) (t_0=HbA1c ~9.3-9.5%)

N=154

  Pre-existing retinopathy & CVD (if not recent/ incapaci-tating) not exclusion factors

  Exclusion of creatinine >1.6 mg/dl, urine albumin >500 mg/d, clinical autonomic neuropathy, & gangrene

Tx: Intensive group to normalize glucose: Evening insulin > add daytime glipizide >insulin BID>multiple insulin shots

Follow-up 27 months. HbA1c difference ~2.1% units

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VA CSDM Endpoints

Cardiovascular Events:

- Amputation (ischemic gangrene)

- CHF

- MI

- Stroke

- CV death

Hypoglycemia:

- Mild: <50 mg/dl or no measurement, but relieved by tx

- Severe: impaired consciousness>3rd party intervention + low glucose or relieved by tx

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VA CSDM Results (1995)

- **Glycemic control achieved & maintained with stepped therapy. HbA1c separation between groups was 2x that in UKPDS, i.e., ~2% units.**

- **61 CV events including 6 CV deaths. Trend for >events in the experimental group:**

  Intensive tx: 35 events/24 pts

  Conventional tx: 26 events/16 pts (p=0.1)

  No events associated with hypoglycemia.

- **LV function not improved**

- **Severe hypoglycemia was rare: 7 events**

  Intensive: 3/100 pt-yrs Conventional: 1/100 pt-yrs

(Abraira 1995, 1997, Pitale 2000)

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Questions

- **Is age the 1° reason the DCCT did not link CVD with glycemic control?**

- **Is there a disconnect between glycemic control & CVD?**

- **Do patients who develop CVD differ from those who do not?**

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Pittsburgh Epidemiology of Diabetes Study (EDC)

- *Prospective Type 1 diabetes cohort*

- Diagnosis before age 18 between 1950-80

- Patients with prior CAD event excluded

- N=603

- Follow-up 10 yrs

- Hard CAD events=CAD death, MI (non-fatal), Q waves, revascularization, stenosis by angio-graphy ($\geq$50%)

(Orchard 2003; Sobel 2003, Pambianco 2006)

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EDC Study: Insulin Resistance in Type 1 & CVD

	No CAD N=495	Angina N=49	ECG Ischemia N=17	Hard CAD N=42
HbA1c (%)	10.4	9.9	10.6	10.7
Triglycerides (mg/dl)	99.8	113.4	145.8	156.5
HDL (mg/dl)	54.8	50.9	51.3	48.3
Creatinine (mg/dl)	0.96	1.03	1.1	1.6
Age at baseline (Yr)	25.9	33.4	32.0	32.9
Duration (Yr)	17.6	25.1	23.4	25.4
Hypertension (%)	9.9	34.7	11.8	42.9
Waist-to-hip ratio	0.82	0.84	0.82	0.86
Depression score	6.8	9.7	3.9	7.7
Glucose disposal (mg/kg/min)	8.1	7.3	7.8	6.4
Glucose disposal (<6.22)	14.1	22.4	18.8	56.1

Glycemic Control & CVD: Ongoing Trials

- **Action to Control Cardiovascular Risk ACCORD (NIH-NHLBI &NIDDK)**

- **Action in Diabetes & Vascular Disease ADVANCE (Institute for International Health)**
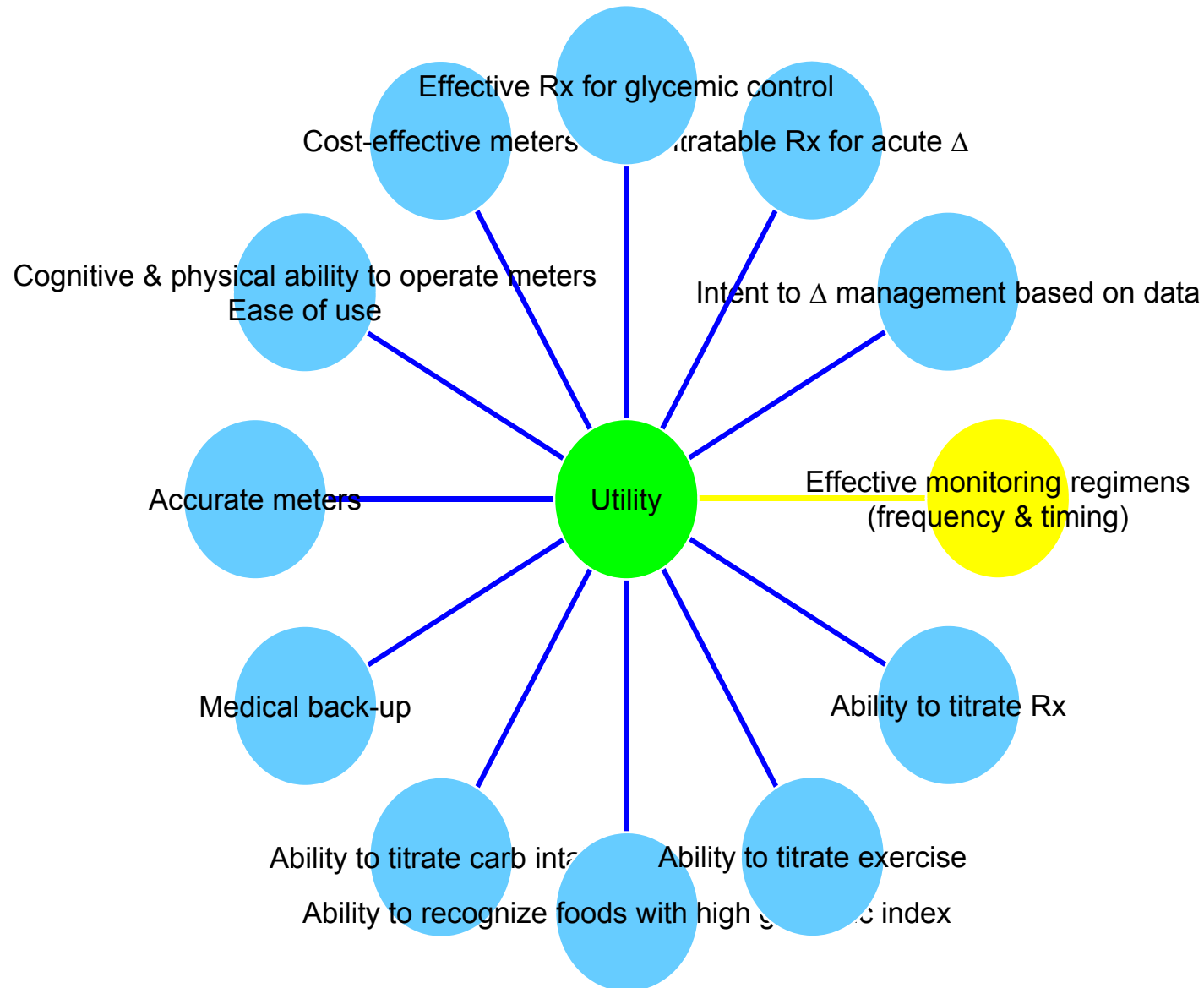
- **Veterans Affairs Diabetes Trial (VADT) (VA)**

Glycemic Control & Glucose Monitoring

What is the role for glucose monitoring older patient populations if:

- Glycemic control does **not** substantially increase **longevity** in older Type 1 patients?

- Glycemic control does **not** prevent/slow the progression of **CVD**, the major cause of mortality & profound morbidity in Type 2 diabetes?

- Glycemic control does **not reverse chronic diabetic complications**?

- Only **33%** of vision loss in Type 2 diabetes (vs 86% in Type 1) is due to **diabetic retinopathy**? (Klein 1984)

- 90% of diabetic retinopathic lesions can be **treated despite** HbA1c level? (Ferris 1993)

- Only 10% of patients with Type 2 diabetes (vs 30-50% in Type 1) **develop diabetic nephropathy** & if **blood pressure control** markedly blunts disease progression,? (Bakris 1993; DeFonzo 1991)

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Elements Contributing to Monitoring Utility

Effective Rx for glycemic control

Cost-effective meters

titratable Rx for acute Δ

Cognitive & physical ability to operate meters
Ease of use

Intent to Δ management based on data

Accurate meters

Utility

Effective monitoring regimens (frequency & timing)

Medical back-up

Ability to titrate Rx

Ability to titrate carb inta

Ability to titrate exercise

Ability to recognize foods with high g   c index

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Glucose Monitoring in Type 2 Diabetes

Multiple observational/X-sectional studies

- **Many based on pharmacy strip refill records**

- **Some older studies used visually read strips instead of reflectance meter readings**

- **Some older studies assessed infrequent SMBG use: 1-4x/month**

Limited # trials w contemporaneous controls

Limited # randomized trials N=11

Limited # blinded trials N=1

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Glucose Monitoring in Type 2 Diabetes

Observational data can be important because:

● **Large populations** can be captured

● **Identify people** not entering randomized trials

● **Identify important** factors/behaviors excluded in randomized trials

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Notable Observational Studies

Soumerai (2004)

Analysis of impact of policy change (providing free meters) in Type 2 patients on insulin (N=1428) & SU (N=1791)

>Insulin users: ~15 strips/mo to ~25 strips/mo

>SU users: ~2 strips/mo to ~10 strips/mo

No improvement in glycemic control except in those with poor glycemic control (HbA1c ~11%). HbAc>~9% in SMBG initiators vs ~9.6% in non-SMBG initiators

Notable Observational Studies

Karter (2001 X-sectional, 2006 longitudinal)

Large HMO data-base with members <65 & >65

Dose-related response to monitoring: 0 vs <1/d, 1x/d, (>3x/d in Type 1) for all groups

Type 2 non-insulin users greatest impact 1st 6 mo

Adherent=ADH Non-Adherent=NON Oral Agents=OA (=N)

	Type 1		Type 2-Insulin		Type 2-OA		Type 2-Diet	
	ADH (395)	NON (764)	ADH (3011)	NON (2541)	ADH (2543)	NON (10,243)	ADH (1987)	NON (2828)
A1c (%)	7.6	8.8	8.2	8.9	8.0	8.7	7.6	8.1

Notable Observational Studies

Evans (1999)

Observational study based on strip refill records

Patients could be using >4 strips/day

Dose-related benefit for strip use in Type 1 patients (N=258)

No dose-related benefit in Type 2 patients using insulin (N=290)

Notable Observational Studies

Martin (2005)

Observational cohort (N=3268)

Patients participating in SMBG had ↑ HbA1c (8.1%>7.2%) than those who did not (7.2%>6.9)

Patients participating in SMBG had ↓ cardiovascular events (5.7% vs 10%) despite ↑ HbA1c values

People participating in SMBG had ↑ # medical visits than those who did not.

Did ↑ # visits > ↑ treatment for blood pressure & lipid management > ↓ CVD?

Glucose Monitoring in Type 2 Diabetes

Observational data can be problematic because of:

HIDDEN SELECTION BIAS:

- Patients with poor control may be <likely to monitor because of discouragement

- Patients with poor control may be >likely to monitor than patients with mild stable disease in an attempt to get their disease under control (Harris 2001)

- Patients who receive more medical care may be more likely to monitor (Martin 2005)

- If patients monitor, they may be considered more compliant & may receive more health provider attention

- If monitoring requires financial expenditures & computer access for down-loading, SES, which is typically associated with better health behaviors/outcomes may come into play

LACK OF BLINDING

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Glucose Monitoring-Randomized Trials: Type 2, Oral Agents/Diet, N >75

Author	Yr	N	Treatment	Results	Comments
Guerci	2003	689	SMBG >6/wk vs None	HbA1c Benefit 0.4%	>40% drop-out
Schwedes	2002	250	SMBG-meal related + counseling vs None	HbA1c Benefit 0.5%	11% drop-out, Not ITT
Fontbonne	1989	208	SMBG vs Urine vs None	NS	21% drop-out
Miles	1997	150	SMBG 1x/d vs Urine 1x/d	NS	24% drop-out, X-over, Unspecified if any insulin users
Davidson	2005	89	Pre/post meal SMBG vs None	NS	Blinded
Rutten	1990	149	SMBG + Medical back-up vs None	NS	NOT RANDOMIZ-ED; >A1c in controls at T=0; monitoring linked w tx regimen

Glucose Monitoring-Randomized Trials: Type 2, Oral Agents/Diet, N <75

Author	Yr	N	Treatment	Results	Comments
Allen	1990	61	SMBG vs Urine	NS	
Estey	1989	60	SMBG +/- Reinforcement	NS	
Wing	1986	50	Monitoring program vs No program	NS	ALSO INSULIN; No separate analysis
Gallichan	1994	27	SMBG vs Urine	NS	
Muchmore	1994	23	SMBG + Carb counting vs Standard education	NS	
Kibriya	1999	64	SMBG 2-3x/d q 2 wks w visits either q 1mo or q 3 mo	NS ? Even better w <support	ALSO INSULIN; No separate analysis; 33% drop-out in intensive arm so replacement, but no ITT

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Continuous Glucose Monitoring

Published randomized trials primarily limited to intermittent continuous glucose monitoring

- **Most recent trials in children & teens
No HbA1c benefit over multiple glucose meter measurements (4-6x/d) (Chase 2005, Deiss 2006, Lagarde 2006, Yates 2006)**

- **Continuous monitoring not better for glycemic control than 8 point fingerstick profile (pre/2 hr post meal, bedtime, 4 AM) in insulin-using adults (Type 1 N=40; Type 2 N=30) (Chico 2003)
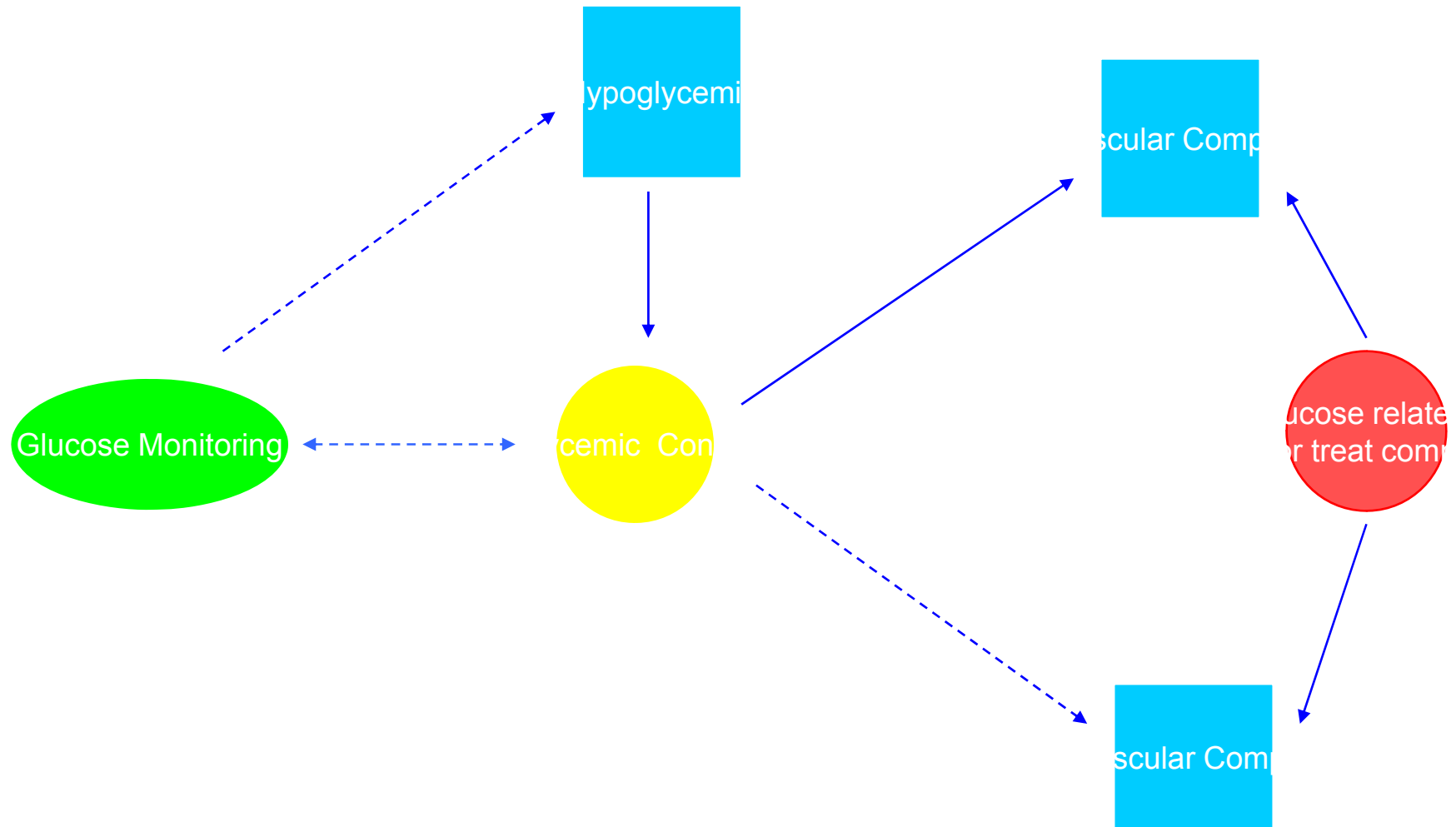Similar results in another randomized trial of insulin-using adults (19-76) (Tanenberg 2004)**

No blinded randomized trials of continuous glucose measurements vs frequent fingerstick monitoring in Type 2 patients >65

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Glucose Monitoring in Type 2 Diabetes: Ongoing Trials

- **Diabetes Glycaemic Education & Monitoring Study**

  DiGEM (UK-National Health Service)

Defining Areas of Current Knowledge

What are priority areas of future research?
Especially for the Medicare population? `