

Treat the Patient, Not the Disease

Edwin Gale



Duality of Interest: None declared

Learning Points

Mind parasites

The risks of growing older

Dialogue with Siegfried

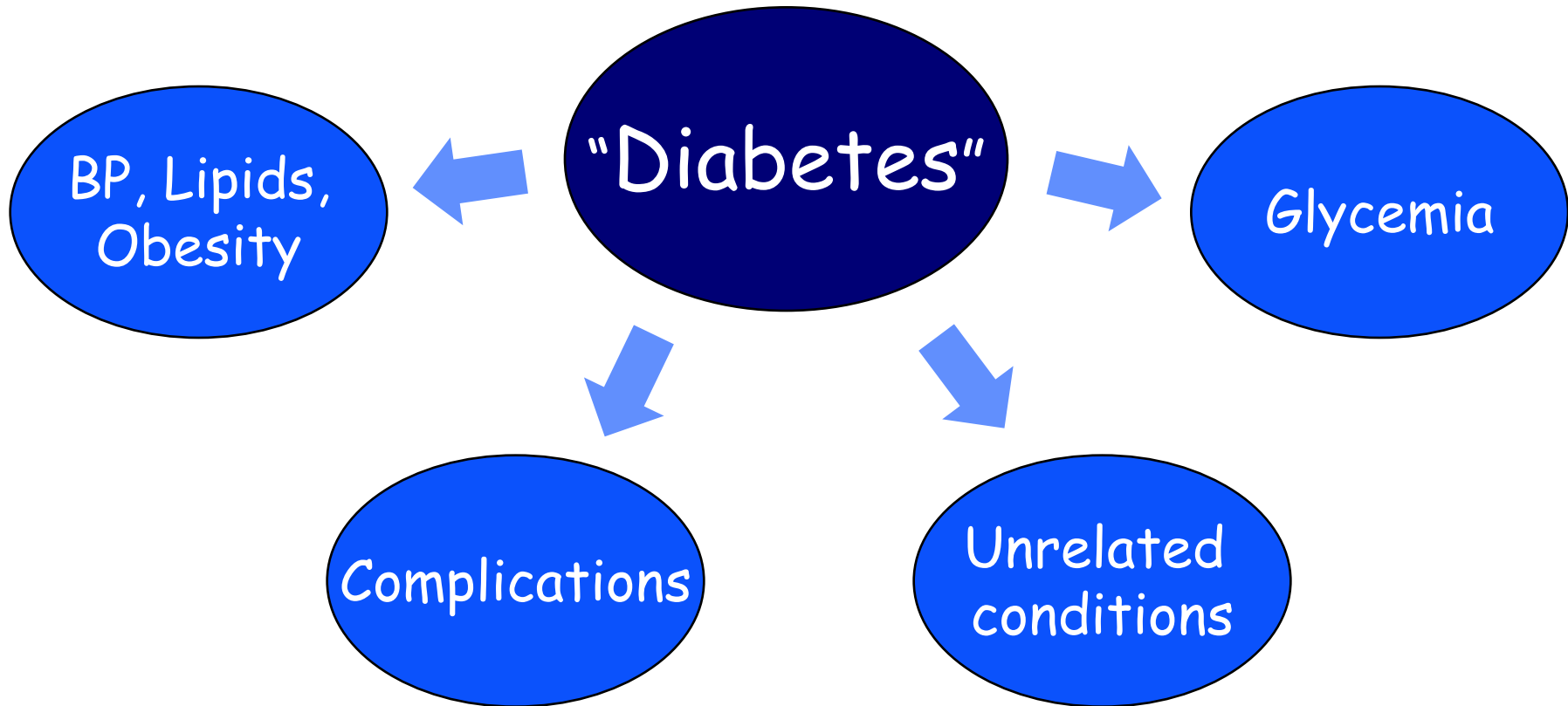
Guidelines and the madness of crowds

Type 1 and type 2 diabetologists

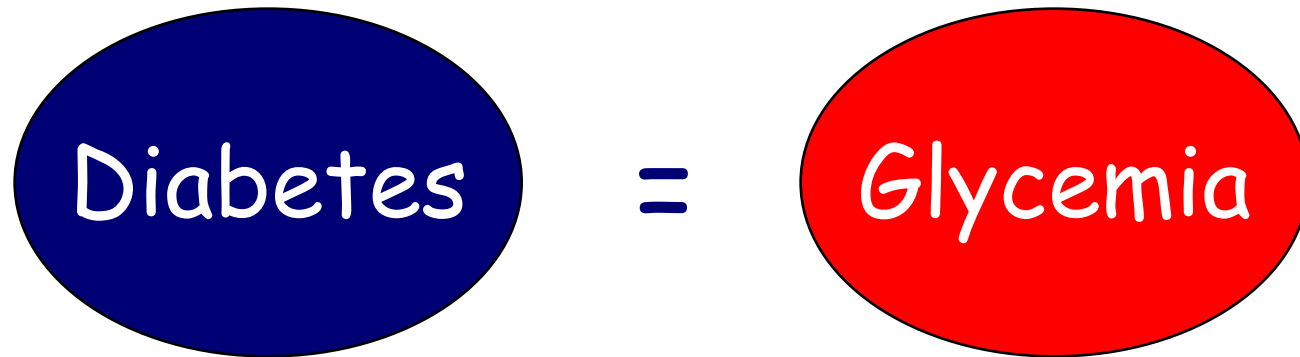
Mind Parasites

A mind parasite is the thought that was in your head before you started to think.

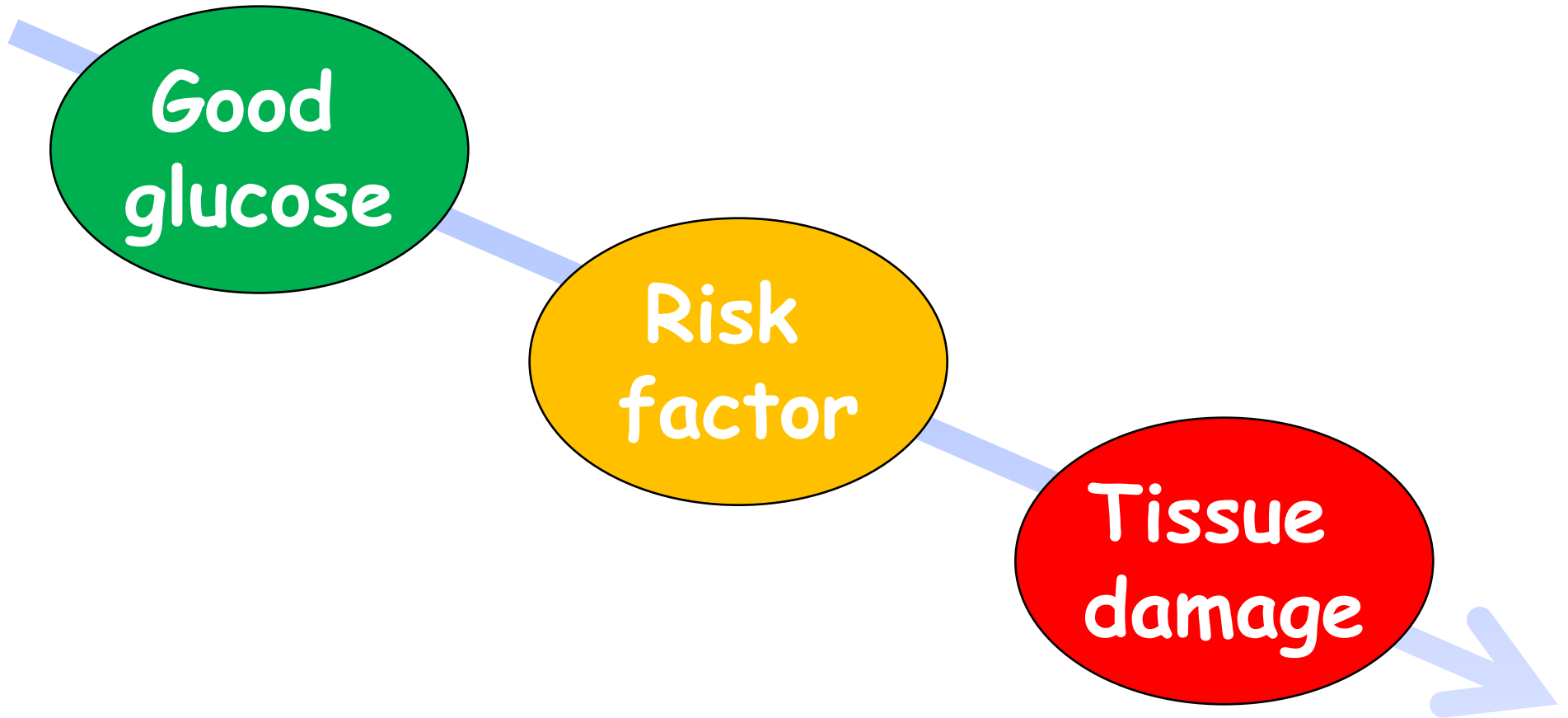
Treating Diabetes



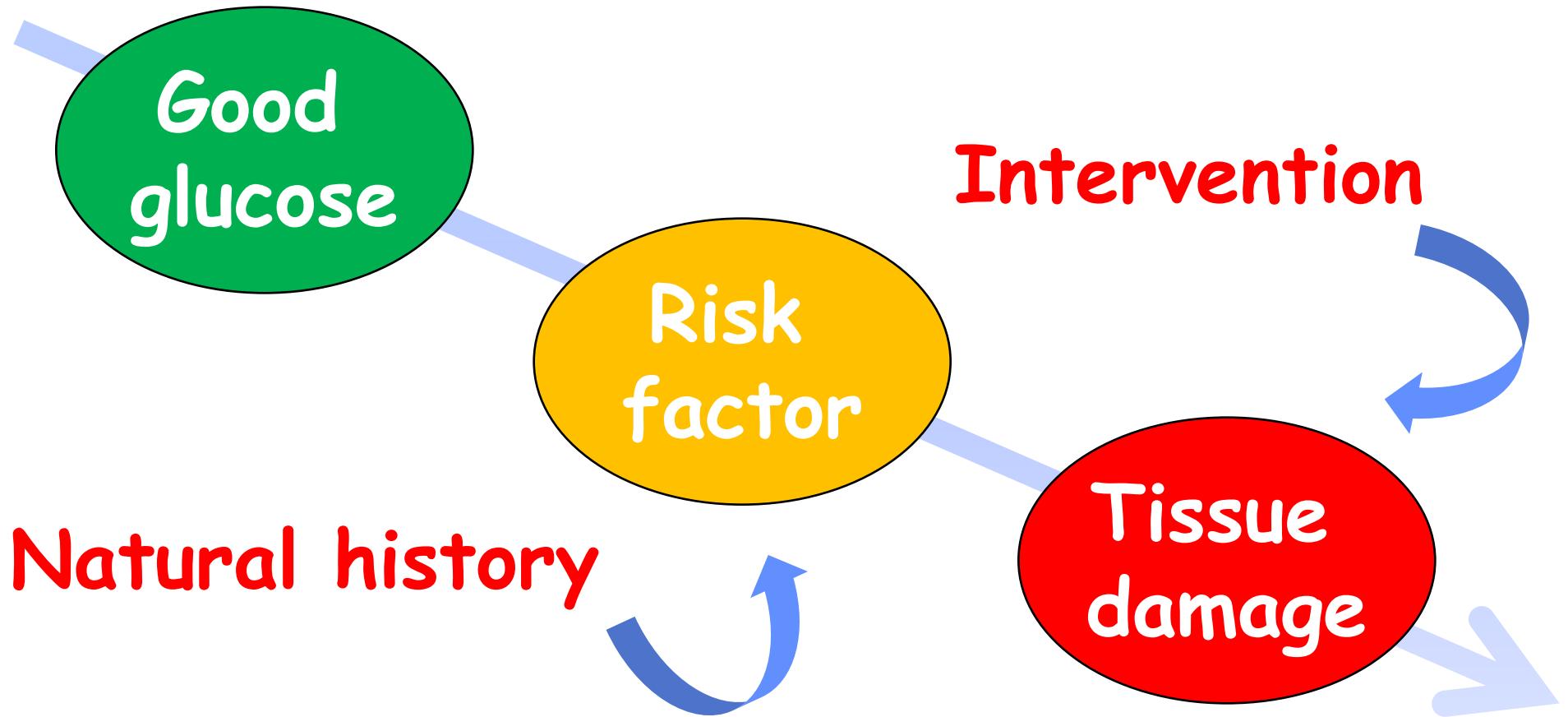
Mind Parasite



When does Blood Glucose become a Disease?



When does Blood Glucose become a Disease?





The aim of glucose management in diabetes is to prevent or minimize adverse glucose-related outcomes

Which Outcomes?

Retinopathy?

Arterial disease?

Non-vascular complications?

Adverse pregnancy outcomes?

Which Outcomes?

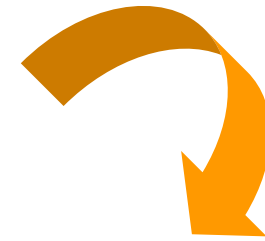
Retinopathy?

Two-hour plasma glucose and vascular risk



Two-hour plasma glucose and vascular risk

Same result
in Arizona,
UK and Egypt



200 mg/dl

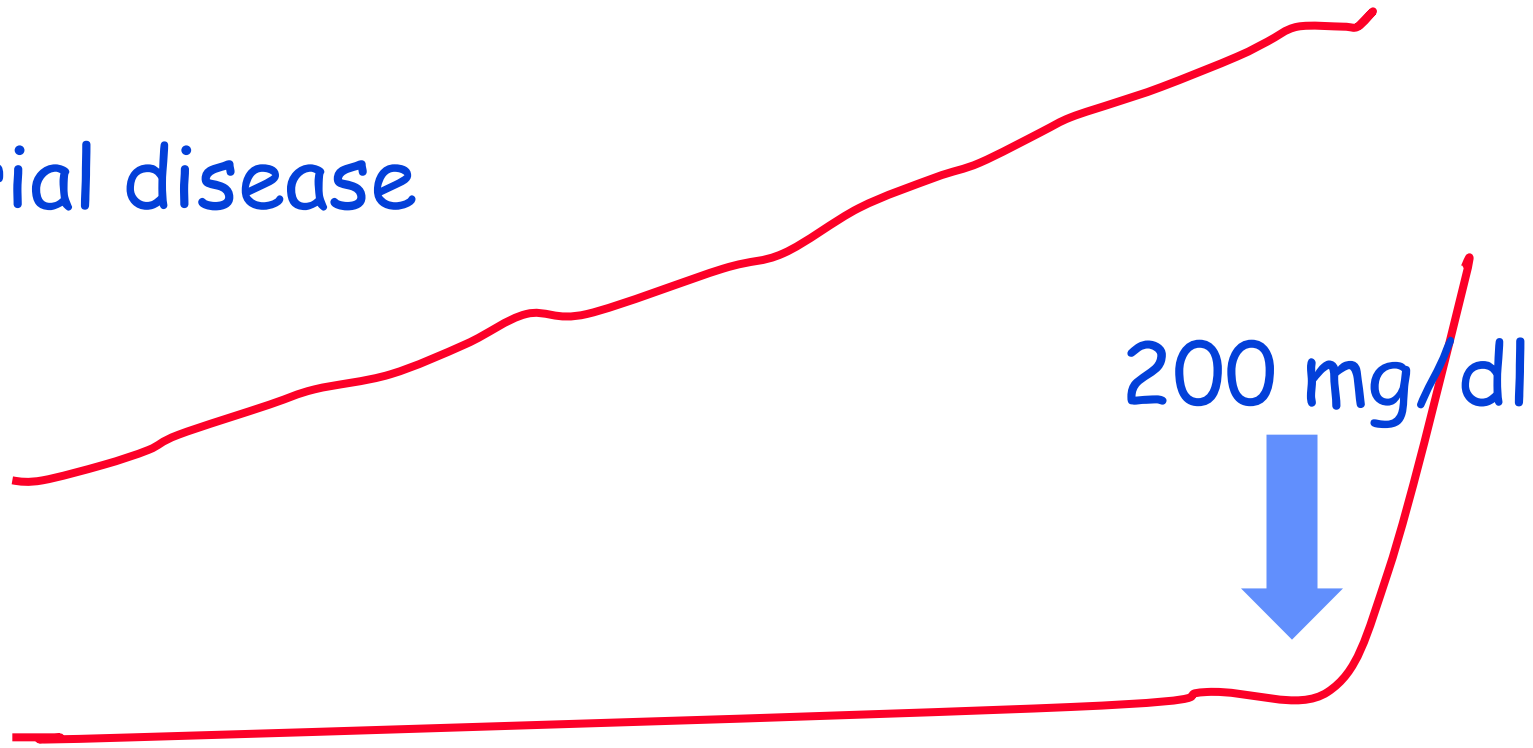


Retinopathy

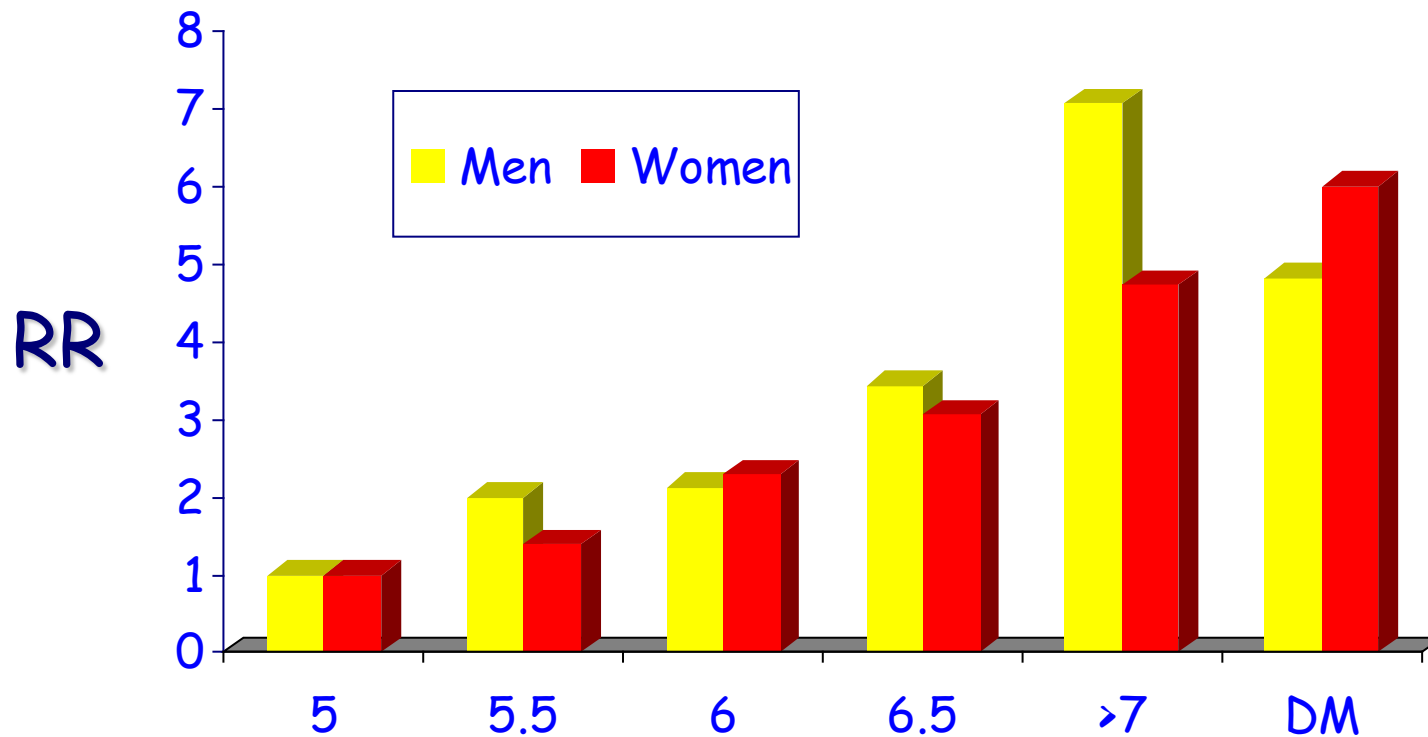


Two-hour plasma glucose and vascular risk

Arterial disease



HbA1c and Coronary Risk in the EPIC Study



Two-hour plasma glucose and arterial risk

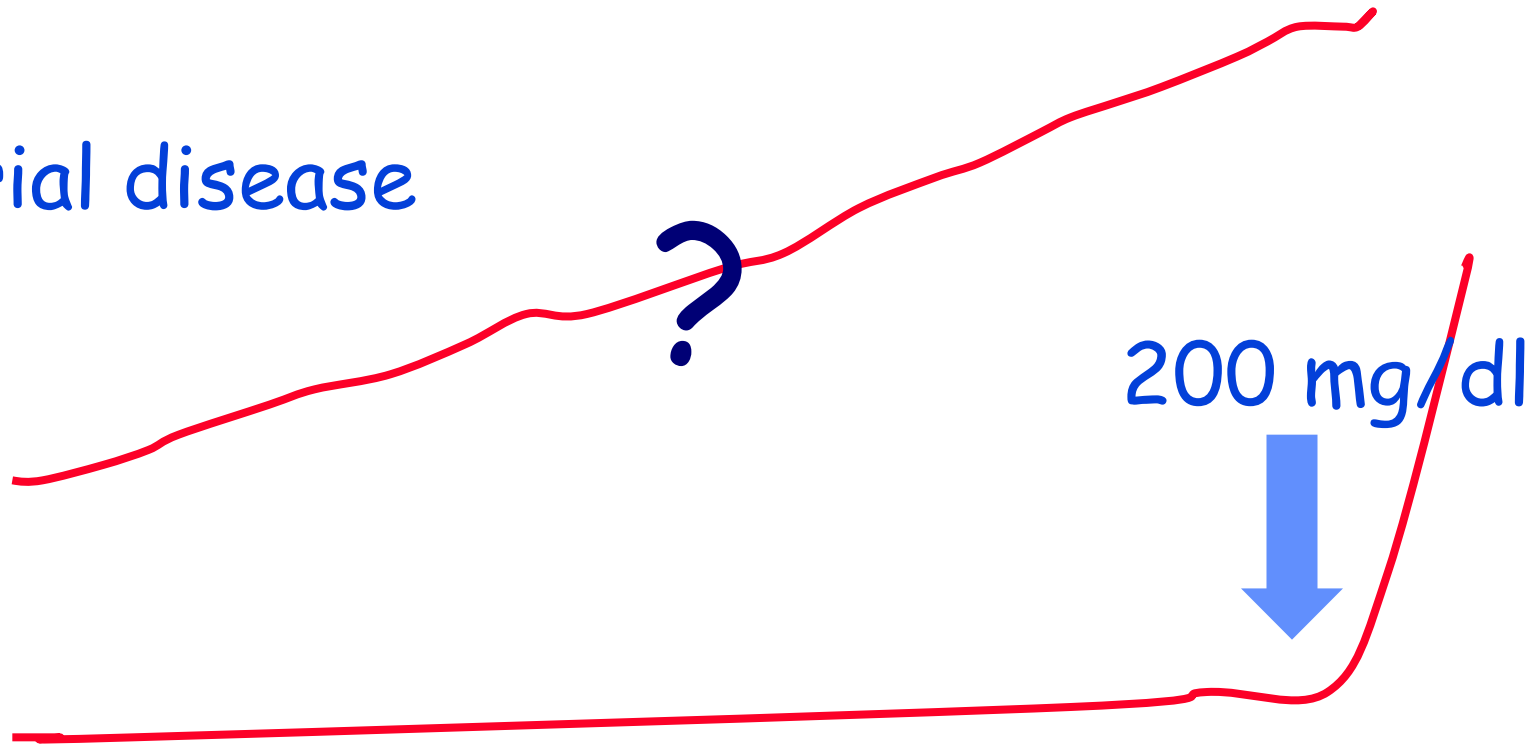
Arterial disease



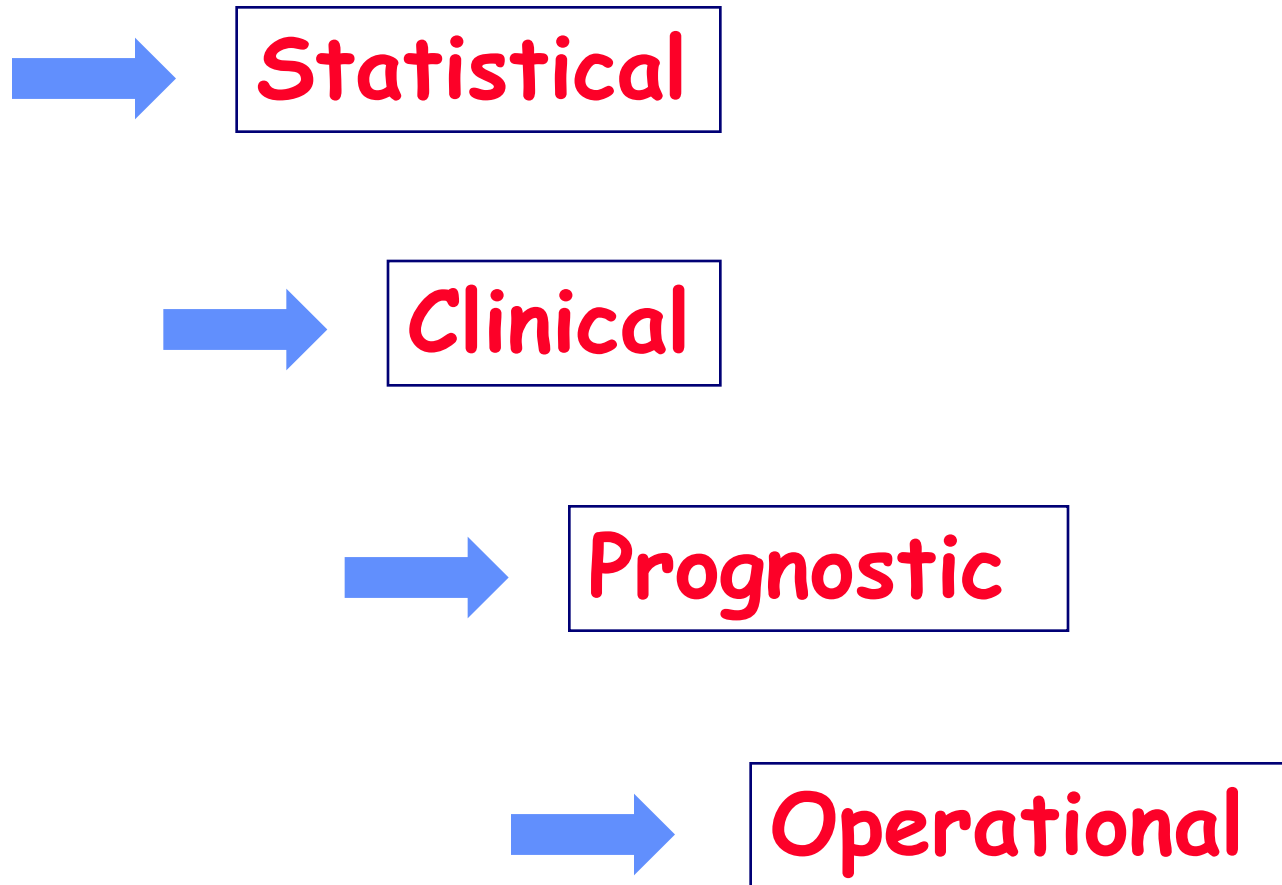
Multiple determinants,
absolute risk varies from
one population to another

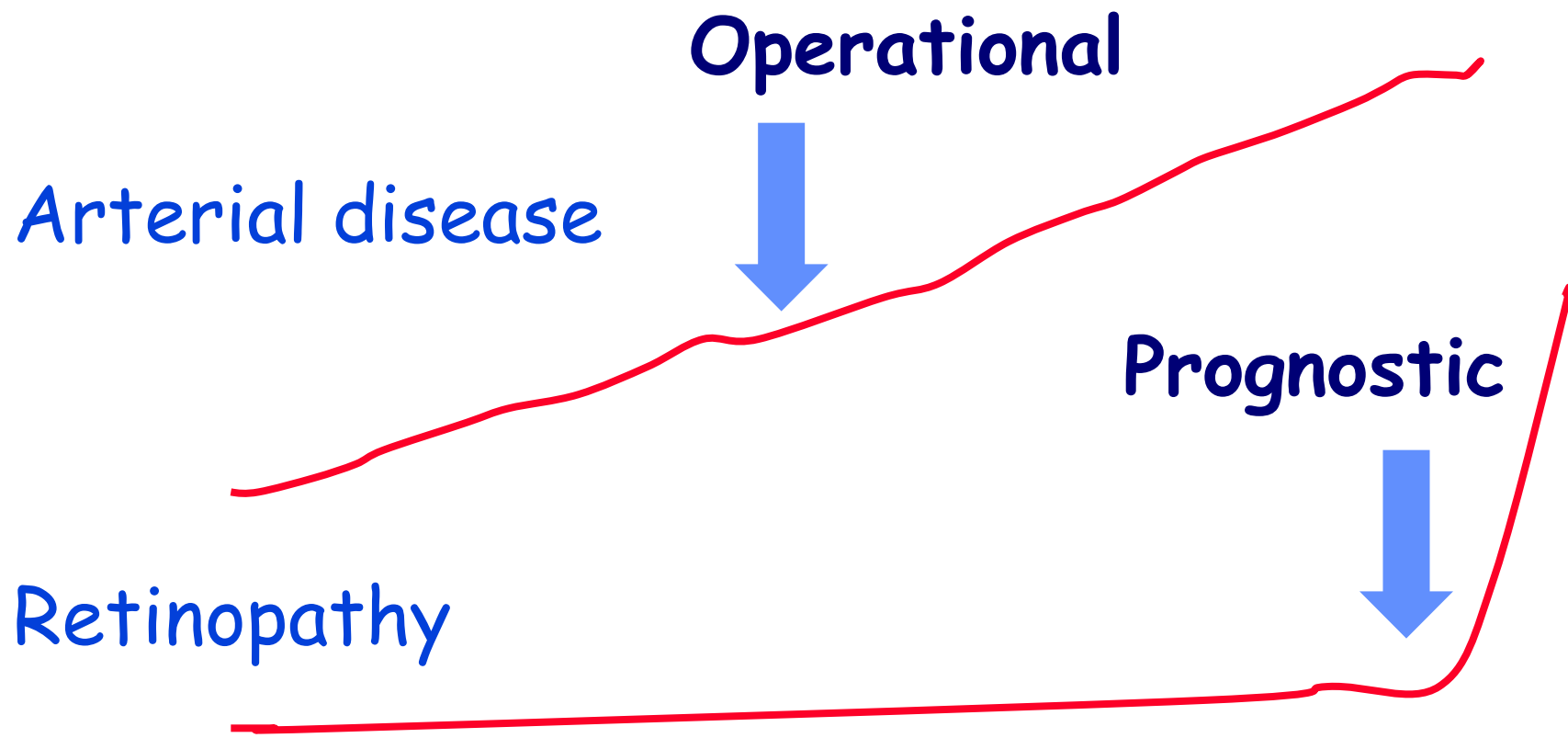
Two-hour plasma glucose and vascular risk

Arterial disease



What is a Cut-Off Point?





Operational

Arterial disease



Prognostic

Retinopathy



Three Questions

1. Is raised glucose (IFG/IGT/HbA1c) a marker of increased cardiovascular risk?

Yes

2. Does this have added value in terms of cardiovascular risk prediction?

Modest only

3. Is there evidence that glucose-lowering therapies reduce cardiovascular risk before the onset of overt diabetes?

No



Conclusion

**Prediabetes is not
a useful diagnosis
to make**

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Type 1 and type 2 diabetologists

The Affluent Phenotype

BP

Lipids

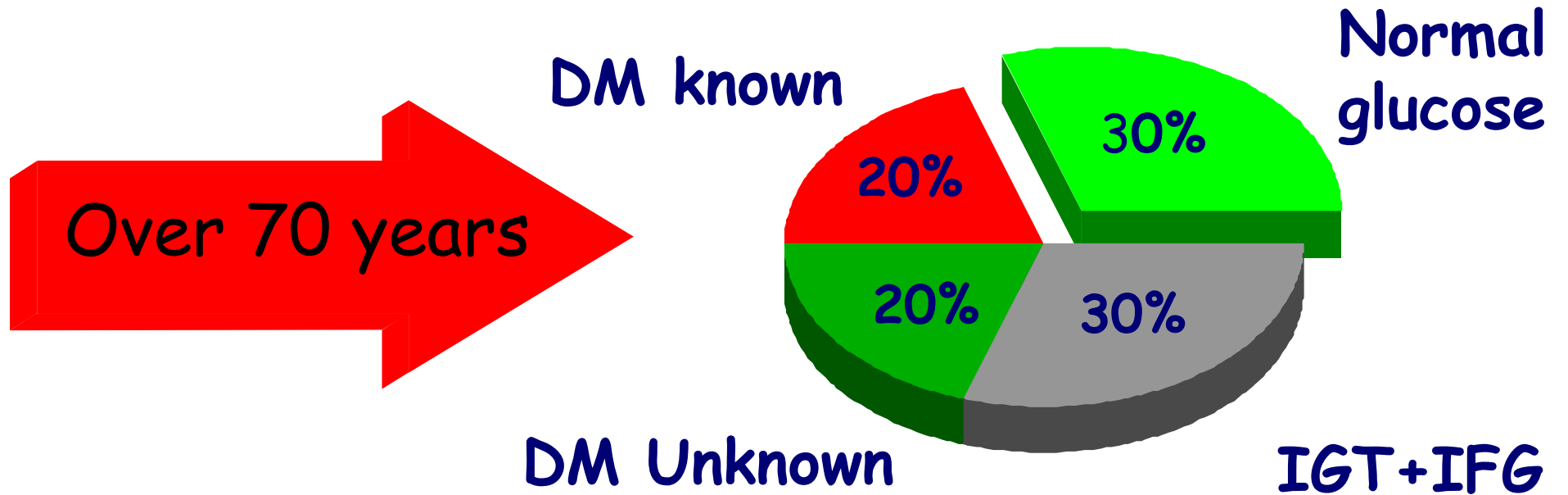
Atheroma

Glucose

Cancer



Lifetime Risk of Hyperglycemia



DECODE

The aim of glucose management in diabetes is to prevent or minimize adverse glucose-related outcomes

Rational management should consider:

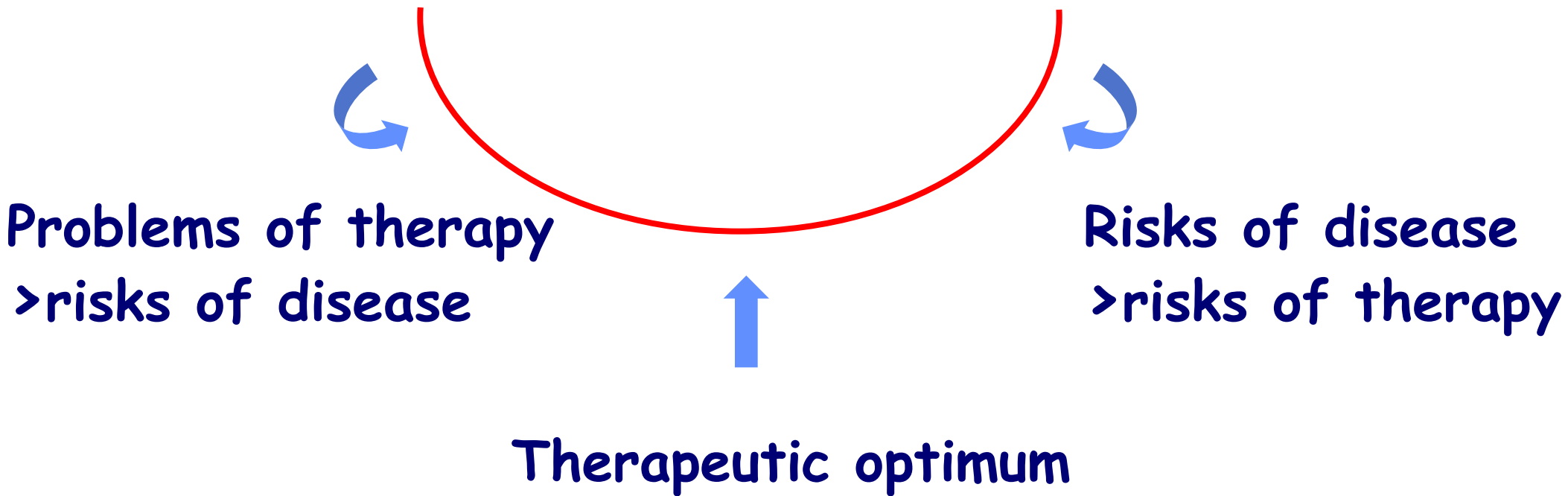
Which outcome?

What degree of risk?

What benefit from intervention?

What disadvantages?

The U-shaped curve



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Type 1 and type 2 diabetologists

Siegfried:

68 years old

Type 2 diabetes for 7 yrs

Active, non-smoker

Angina, hypertension,
osteoarthritis

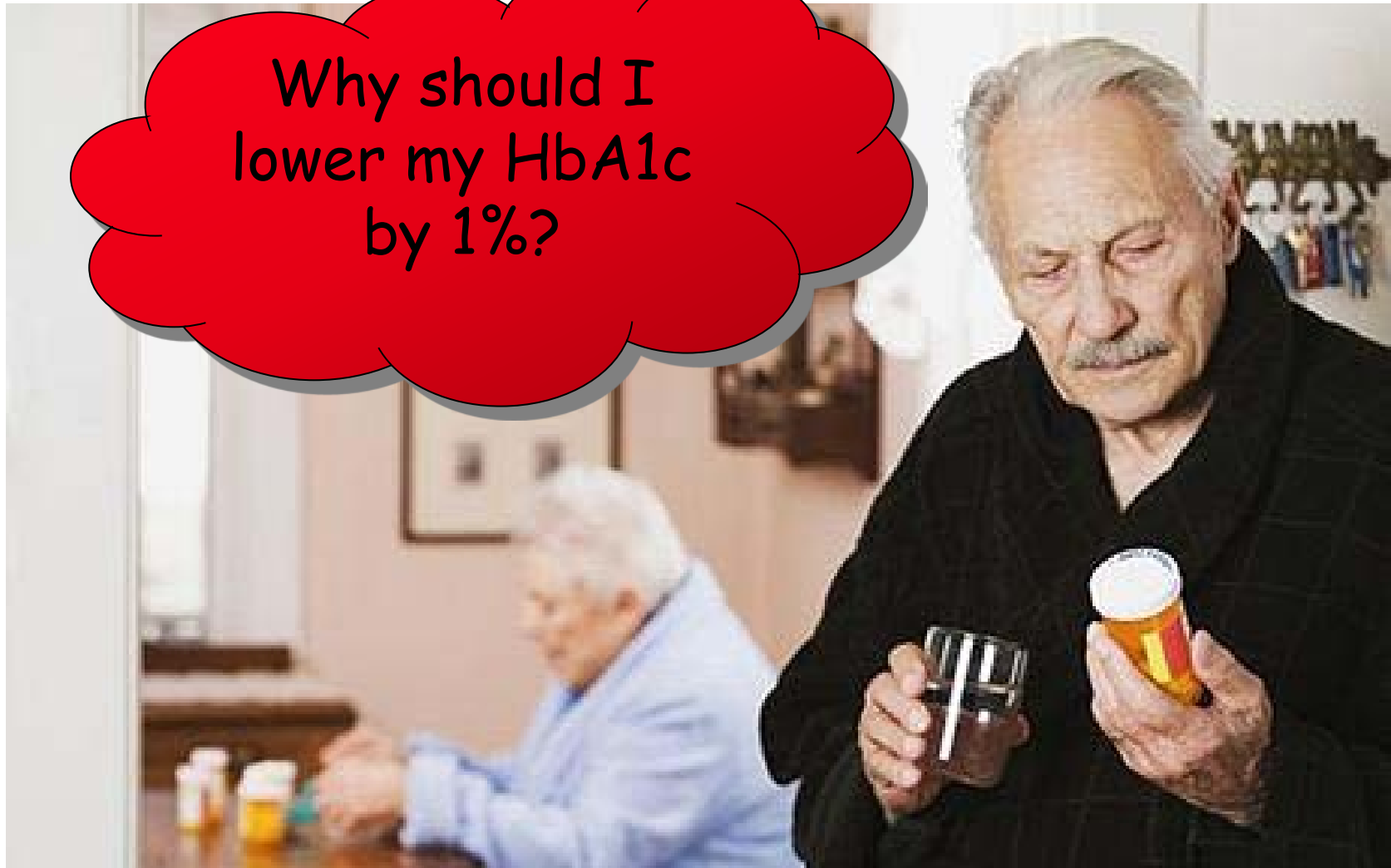


R_x

Metformin, aspirin,
ACE inhibitor, statin,
nitrates

HbA1c: 8.2%

Why should I
lower my HbA1c
by 1%?



Intensive Glycemic Control and the Prevention of Cardiovascular Events: Implications of the ACCORD, ADVANCE, and VA Diabetes Trials

A position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association

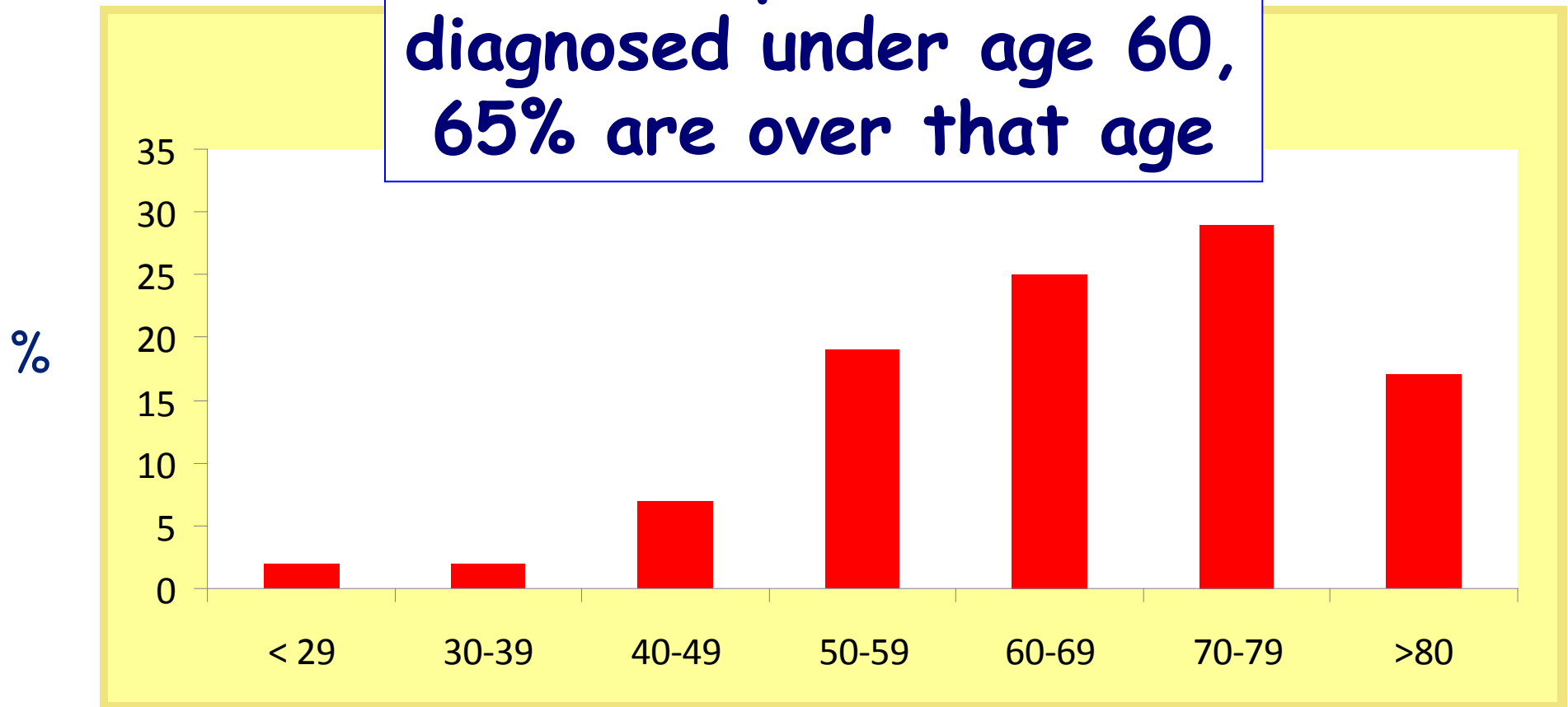
“Until more evidence becomes available, the general goal of <7% appears reasonable”

But does your
evidence apply
to me?



How Representative is Siegfried?

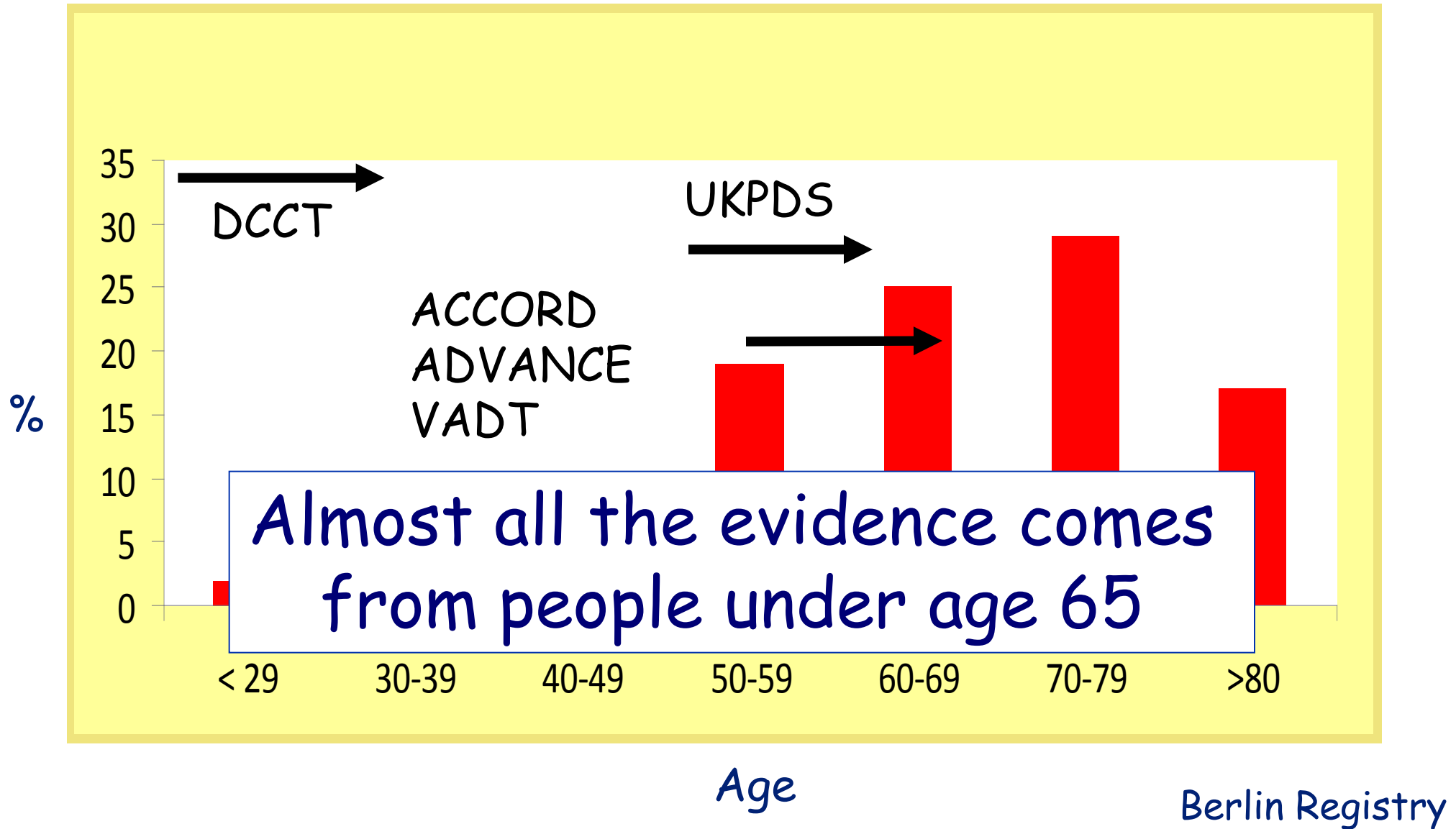
50% of patients are diagnosed under age 60, 65% are over that age



Age

Berlin Registry

The Evidence Distribution



A red, cloud-like shape with a drop shadow, containing the text 'Some questions' in a dark blue, sans-serif font.

Some questions

- Will I feel better?
- Will I live longer?
- Will I experience fewer complications?
- What's the down side?
- Are there alternatives?

Patient perceptions of intensive glucose lowering

701 pts with T2DM asked re QOL utilities;
a score of 1.0 = perfect health, 0 = death

Intensive glucose control scored 0.67, or 1/3 of
a year's quality of life

Patient and physician perceptions of diabetes care >65 years of age

One third estimated by physicians to have a life expectancy < 5 years (patients more optimistic!)

10-18% of patients considered diabetes treatment a major imposition

“Few physicians had patients with homogeneous clinical characteristics”

“Older diabetic patients with multiple comorbidities are complex and frequently a poor fit for clinical practice guidelines designed for younger people”

Will I live longer?

Will I feel better?

• Will I live longer?

• Will I experience fewer complications?

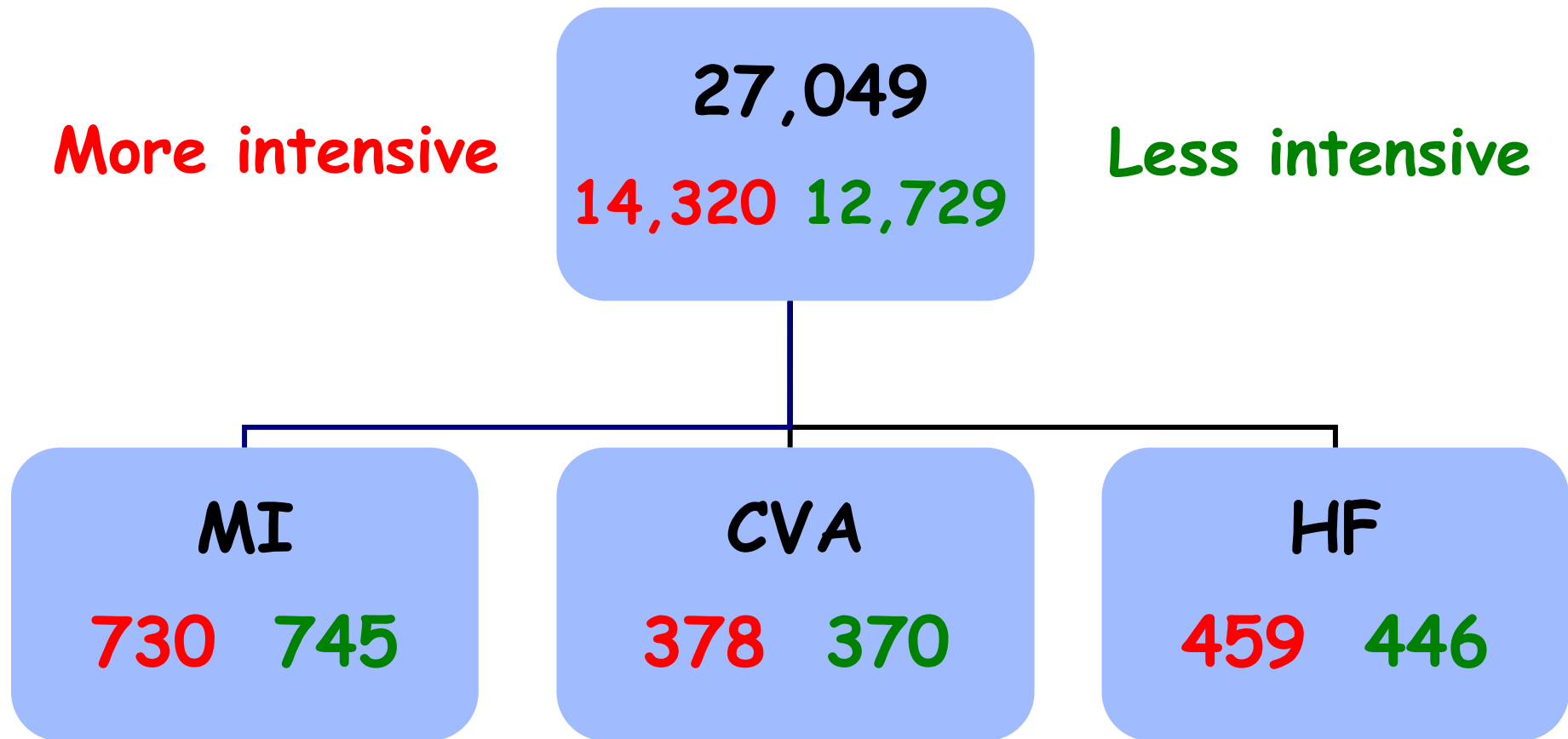
• What's the down side?

• Are there better alternatives?

Comorbidity and Glucose Control, New onset patients aged 60-64 yrs

	Comorb.	Life Expect.	Days added
Case 1	0	14.6 yrs	+106
Case 2	3	9.7 yrs	+ 44
Case 3	7	4.8 yrs	+ 8

Glucose Control and Macrovascular Outcomes

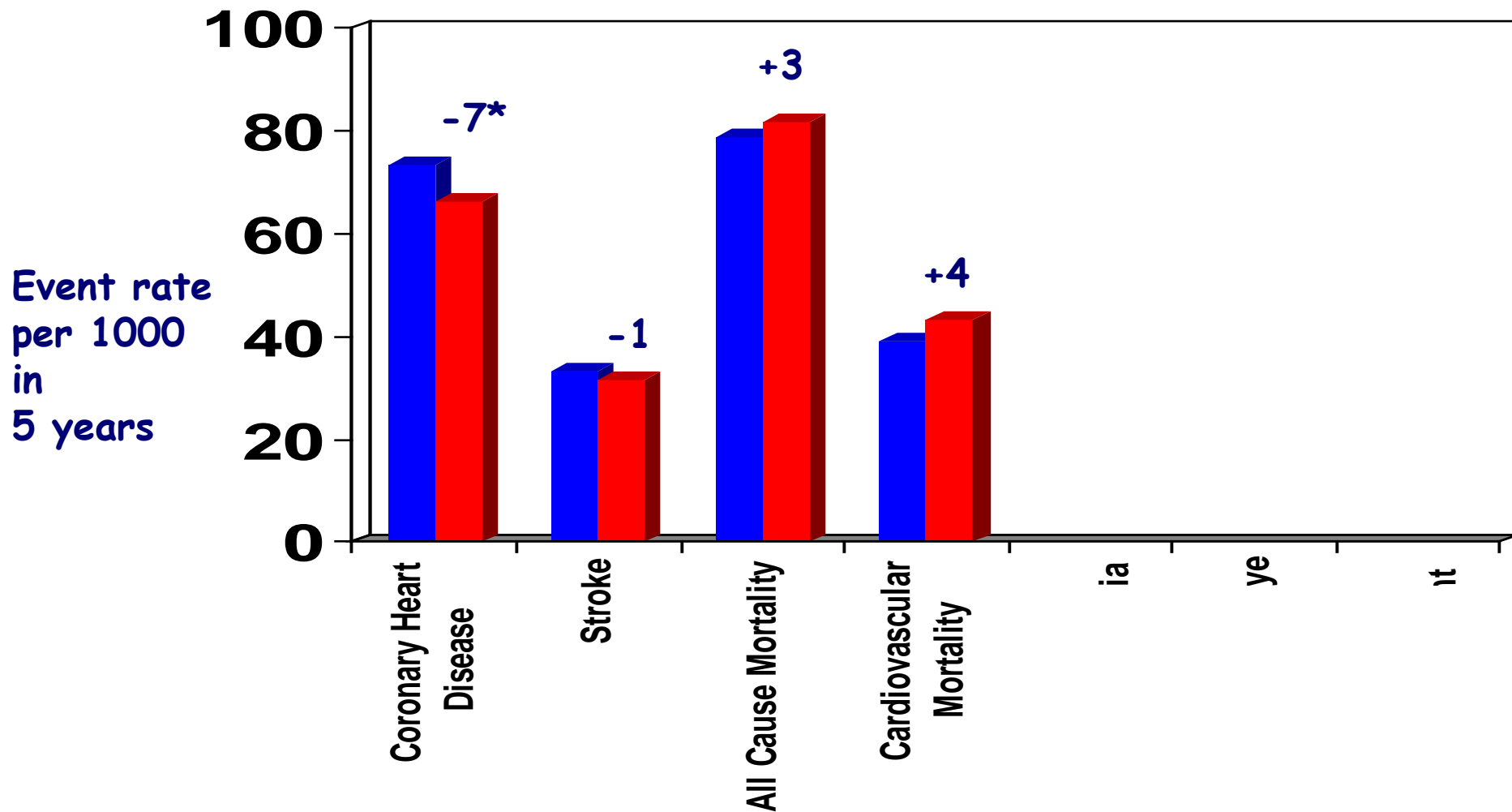


Outcomes per 1000 patients/~4.5 yr

	Intensive	Conventional
MI	51	59*
CVA	26	29
HF	32	35
CV deaths	34	35
All deaths	68	69

Risk-Benefit Ratio

- For every 140 people put on intensive glucose control and monitoring for 5 years, one will benefit
- The event prevented will be a non-fatal myocardial infarct



NNT 5 years

140

768

329

259

**Will I experience
fewer
microvascular
complications?**

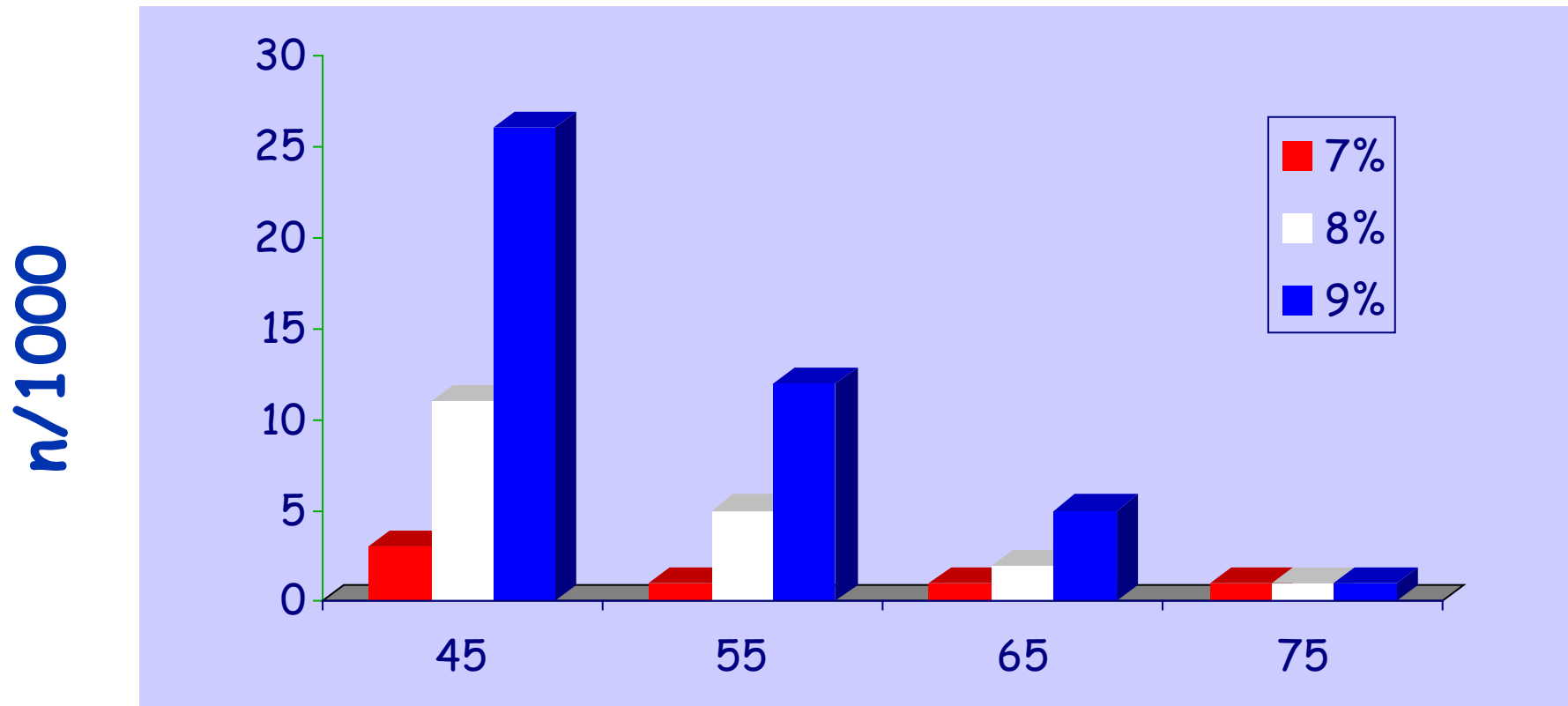
Will I feel better?

Will I live longer?

Will I experience fewer
complications?

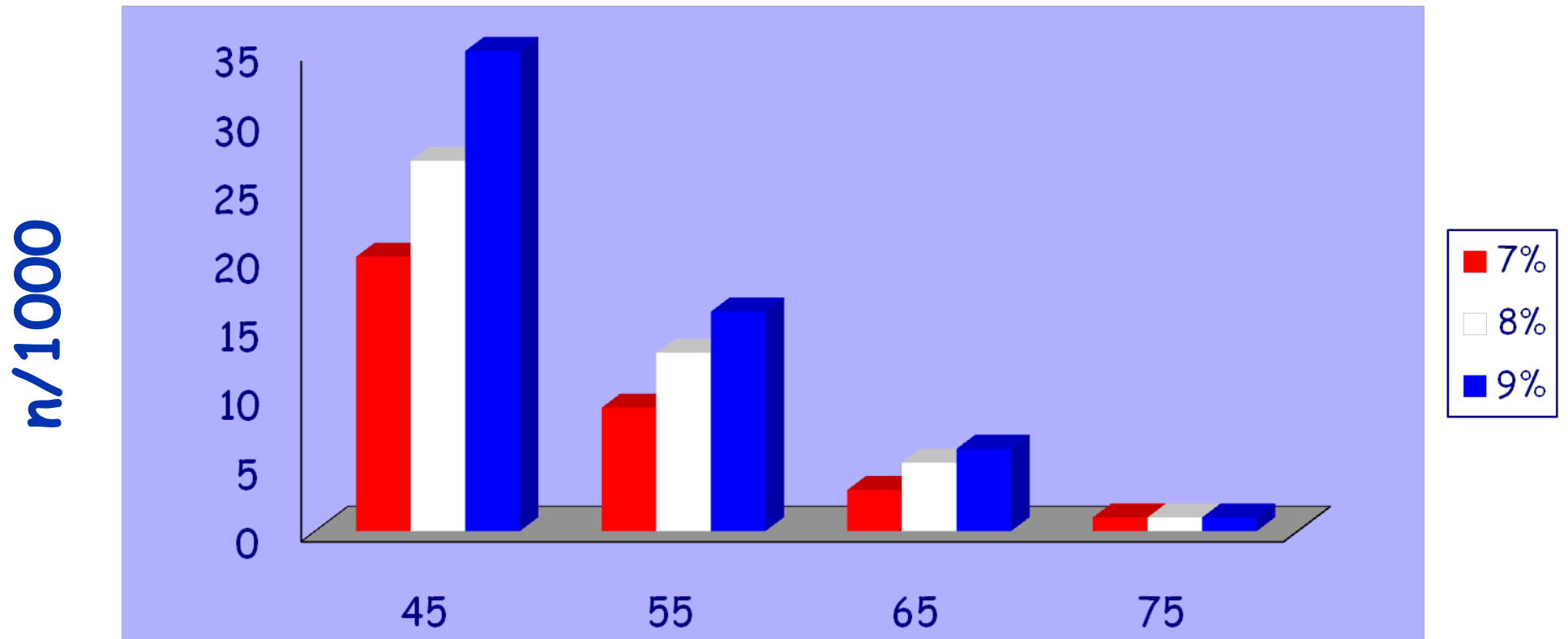
- What's the down side?
- Are there better alternatives?

Lifetime Risk of Blindness by Age at Diagnosis and HbA1c



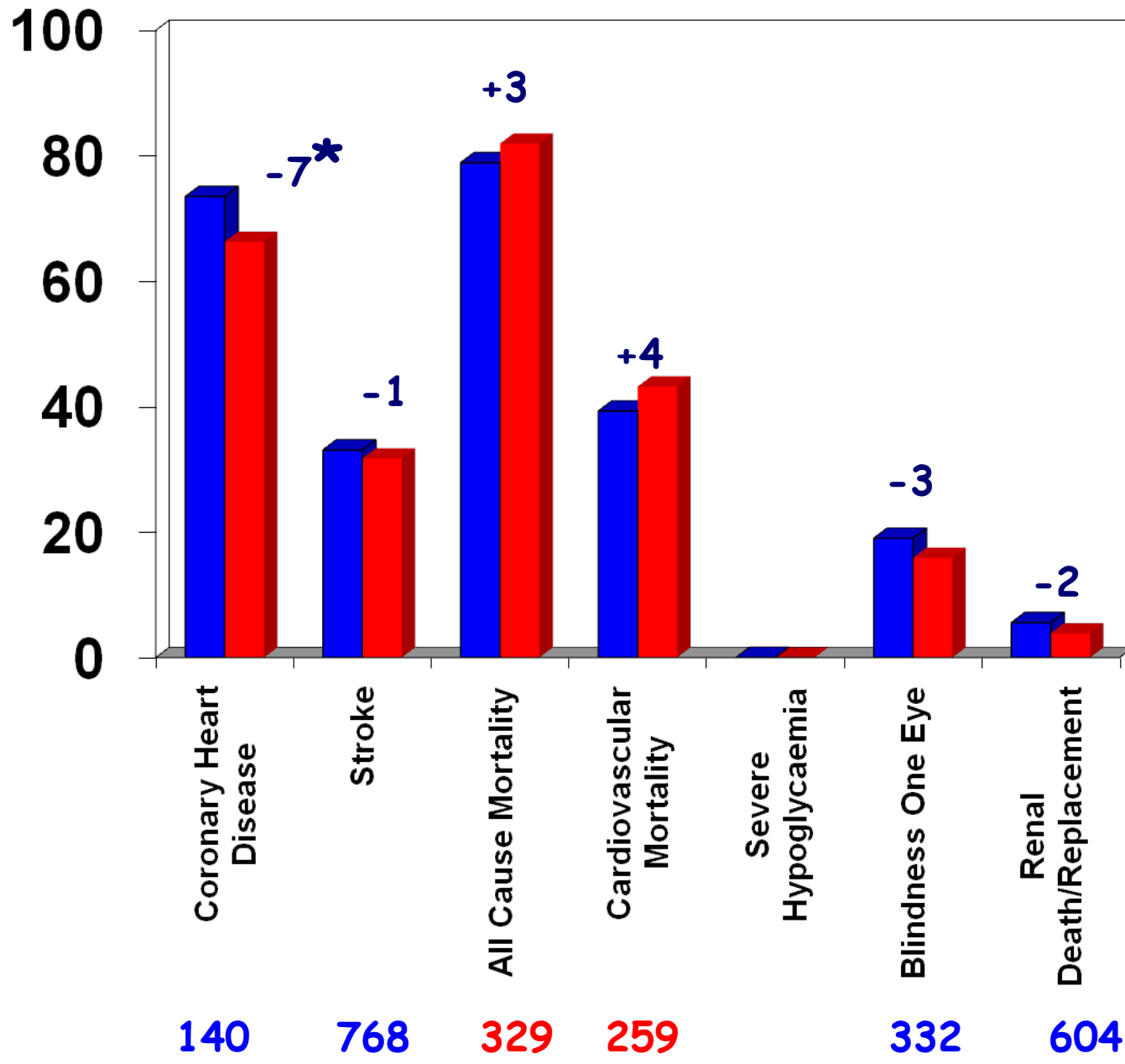
Age at diagnosis

Lifetime Risk of ESRF by Age at Diagnosis and HbA1c



Age at diagnosis

Event rate
per 1000
in 5 years



NNT 5 years



**What's the down
side?**

- Will I feel better?
- Will I live longer?
- Will I experience fewer complications?
- What's the down side?
- Are there better alternatives?

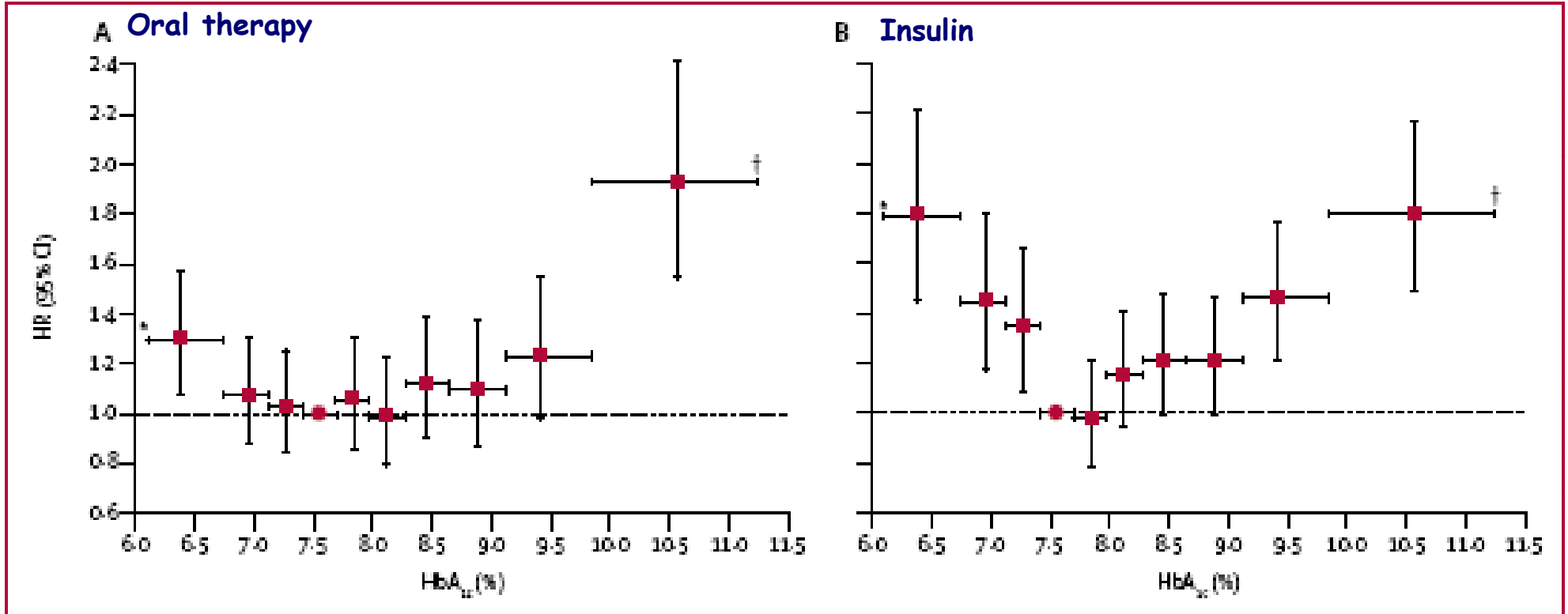
Hypos per 1000 patients/~5 yr

	Intensive	Conventional
Hypos	75*	29

Wt gain per 1000 patients/~3.5 yr

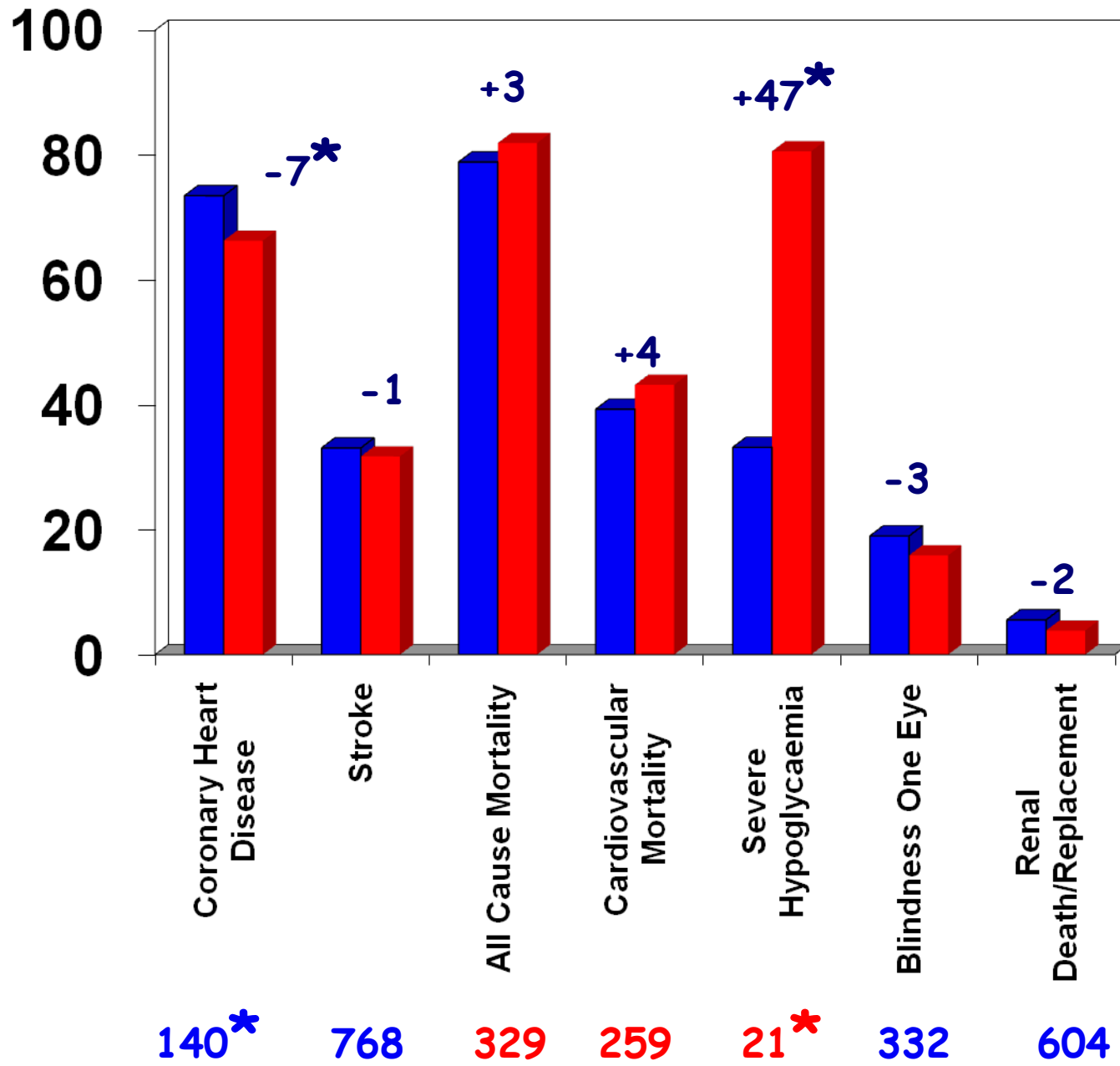
	Intensive	Conventional
Wt gain >10kg	276*	141

HbA1c and Mortality in 47,970 Patients



UK General Practice Research Database,
Currie et al, Lancet 2010

Event rate
per 1000
in 5 years



NNT 5 years



Are there better alternatives?

- Will I feel better?
- Will I live longer?
- Will I experience fewer complications?
- What's the down side?
- Are there better alternatives?

Numbers Needed to Treat [To prevent 1 CVD event]

Glucose (HbA1c 0.9%) : 140

Cholesterol trials (1mM) 44

Blood Pressure trials (10/6mmHg) 34

STENO-2

NEJM 2008;358:580

Randomized

160

80

80

Trial Ends

67

63

Mean 7.8 yr

Study Ends

55

38

Mean 5.5 yr

Died

24 (9 CVD)

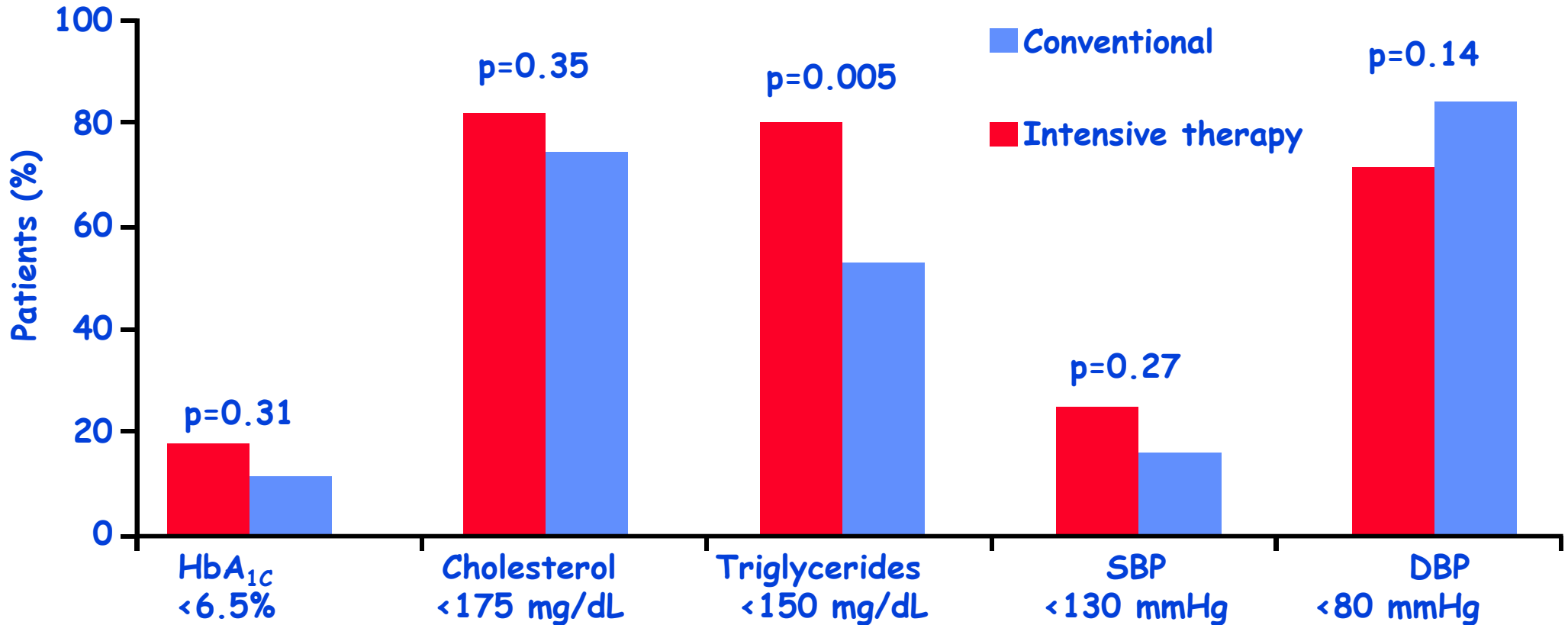
40 (19 CVD)

Intensified
(1 dropped out)

Conventional
(2 dropped out)

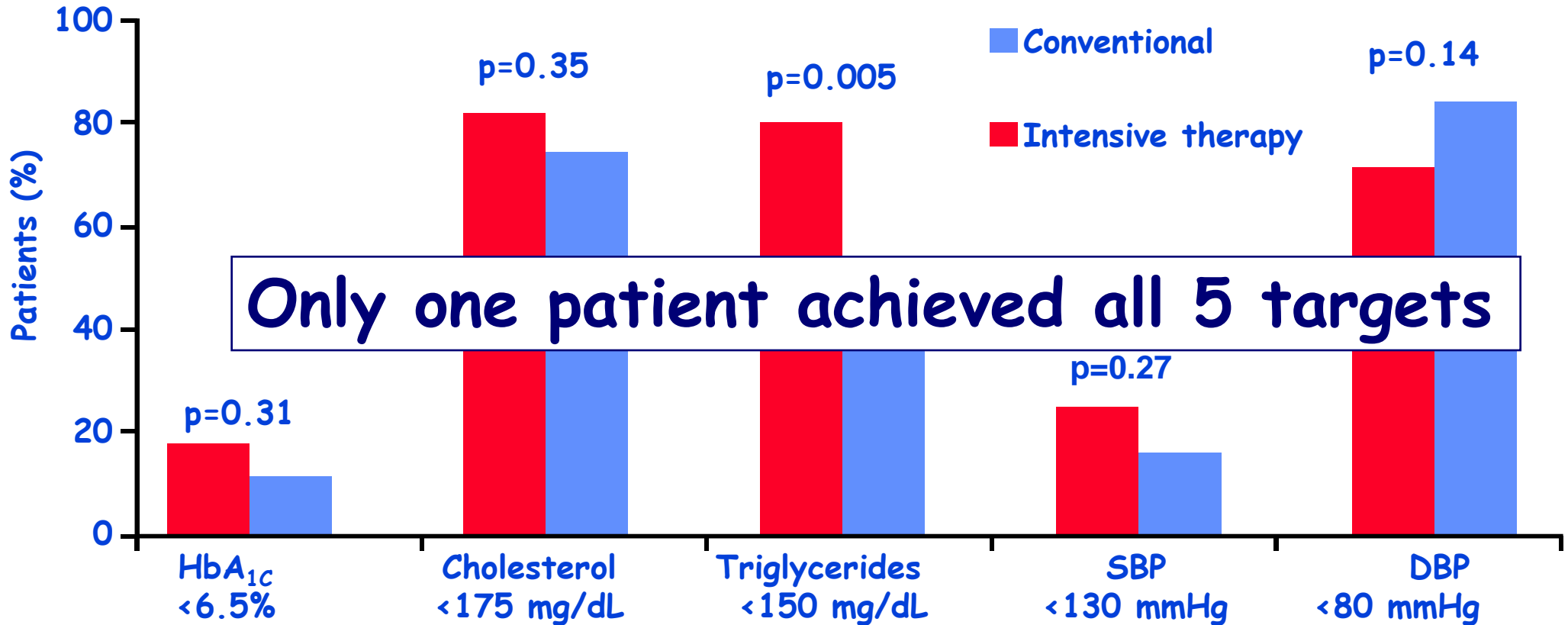
Percentage of patients reaching target

Patients at goal in STENO-2



Percentage of patients reaching target

Patients at goal in STENO-2



A red, cloud-like shape with a drop shadow, containing the text "Some answers".

Some answers

- I will not feel better
- I will not live longer
- I will experience fewer microvascular complications
- But a lot more side effects
- And there are better alternatives

Thanks, I'll call
you later



Learning Points

Mind parasites

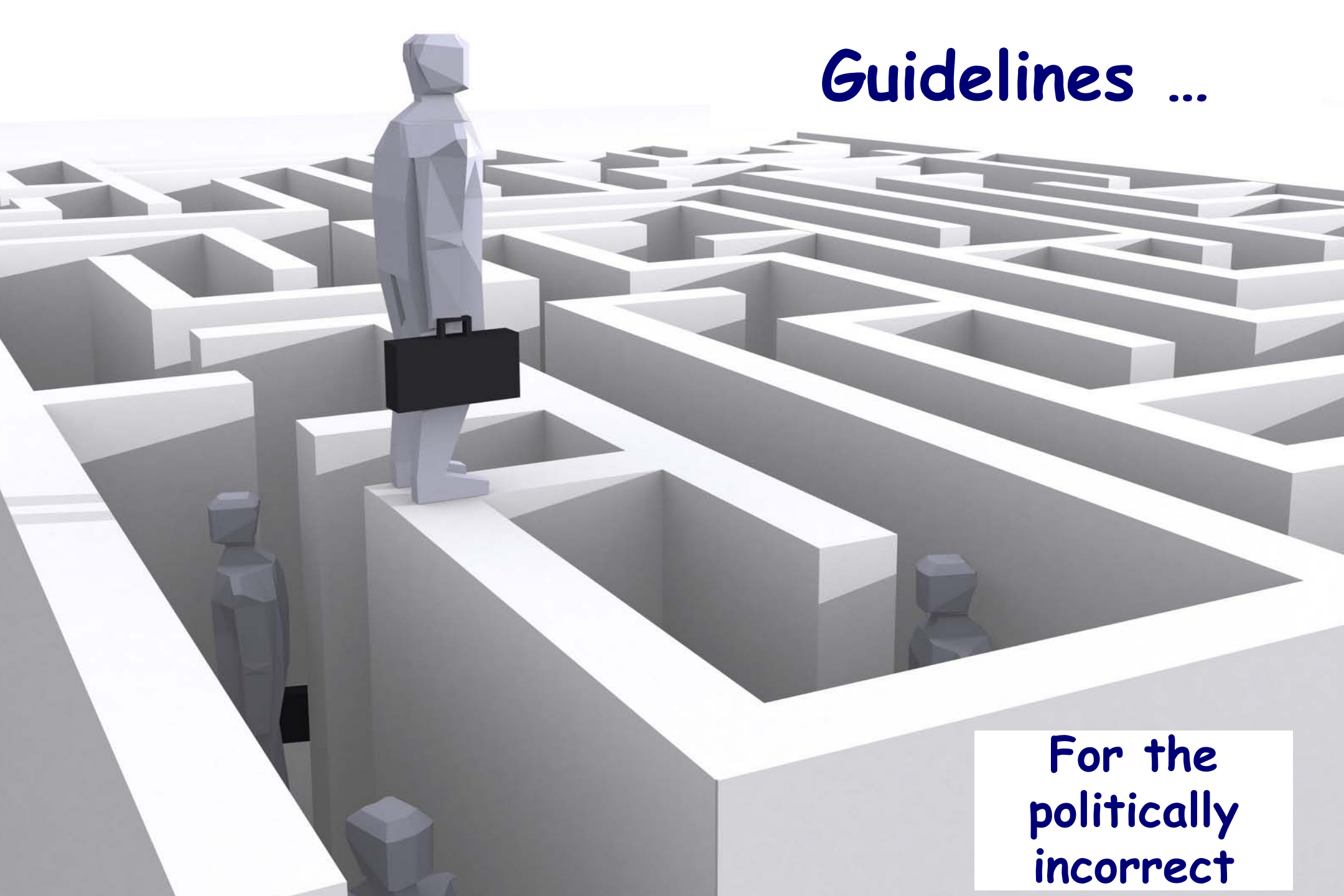
The risks of growing older

Dialogue with Siegfried

Guidelines and the madness of crowds

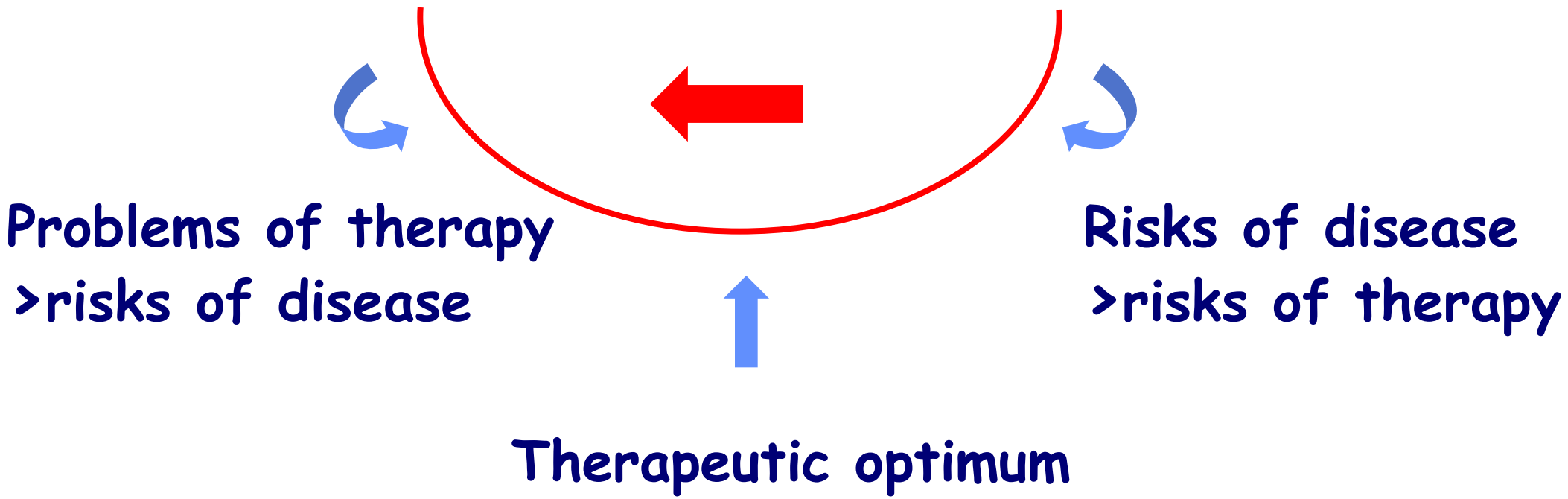
Type 1 and type 2 diabetologists

Guidelines ...



**For the
politically
incorrect**

**Bad guidelines promote overdiagnosis
and overtreatment**



The Pathology of Guidelines

1. Guidelines that have a political agenda
2. Guidelines that claim to be evidence based
3. Guidelines that aspire to the point of therapeutic futility

Why Guidelines are Issued:

1. The Angelic version



Guidelines help doctors to offer the best, safest and most cost-effective treatment to their patients

They are issued as a service to humanity

Why Guidelines are Issued:

2. The Satanic version



Guidelines are a statement of authority

They assert the right of competing organizations
to legislate for the diabetes community

**“Guidelines are a
Statement of Authority”**

**Do you doubt
this assertion?**

Then ask yourself this question:





Are guidelines judged according
to their scientific quality?

... or according to the status of the
organization that issued them?



**Are guidelines judged according
to their scientific quality?**

**... or according to the status of the
organization that issued them?**

"The Satanic version"



There are 3 types of guideline:

Ontological
Territorial
Imperial

The Ontological Guideline:



"I think, therefore I exist"

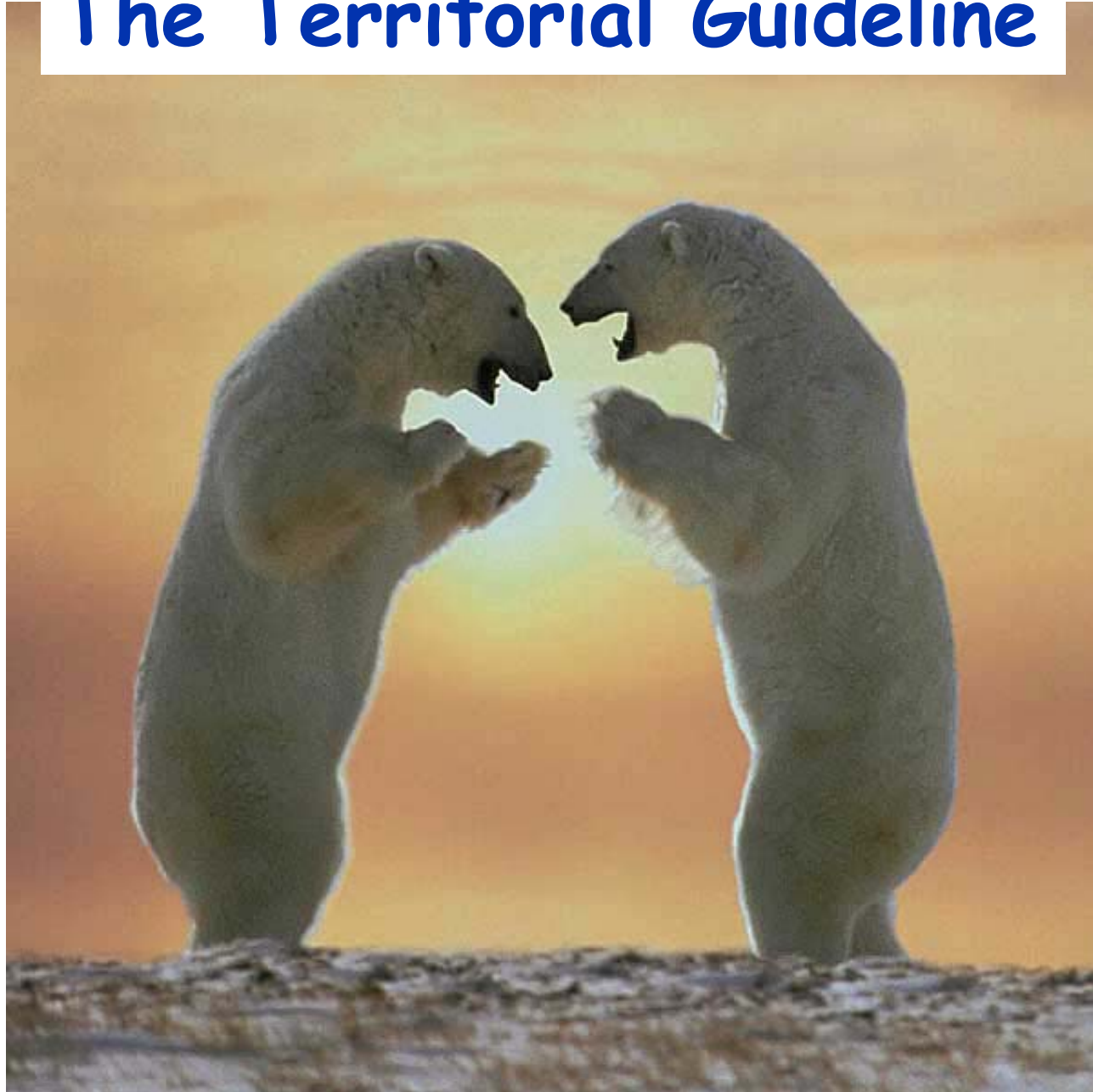
René Descartes

The Ontological Guideline:

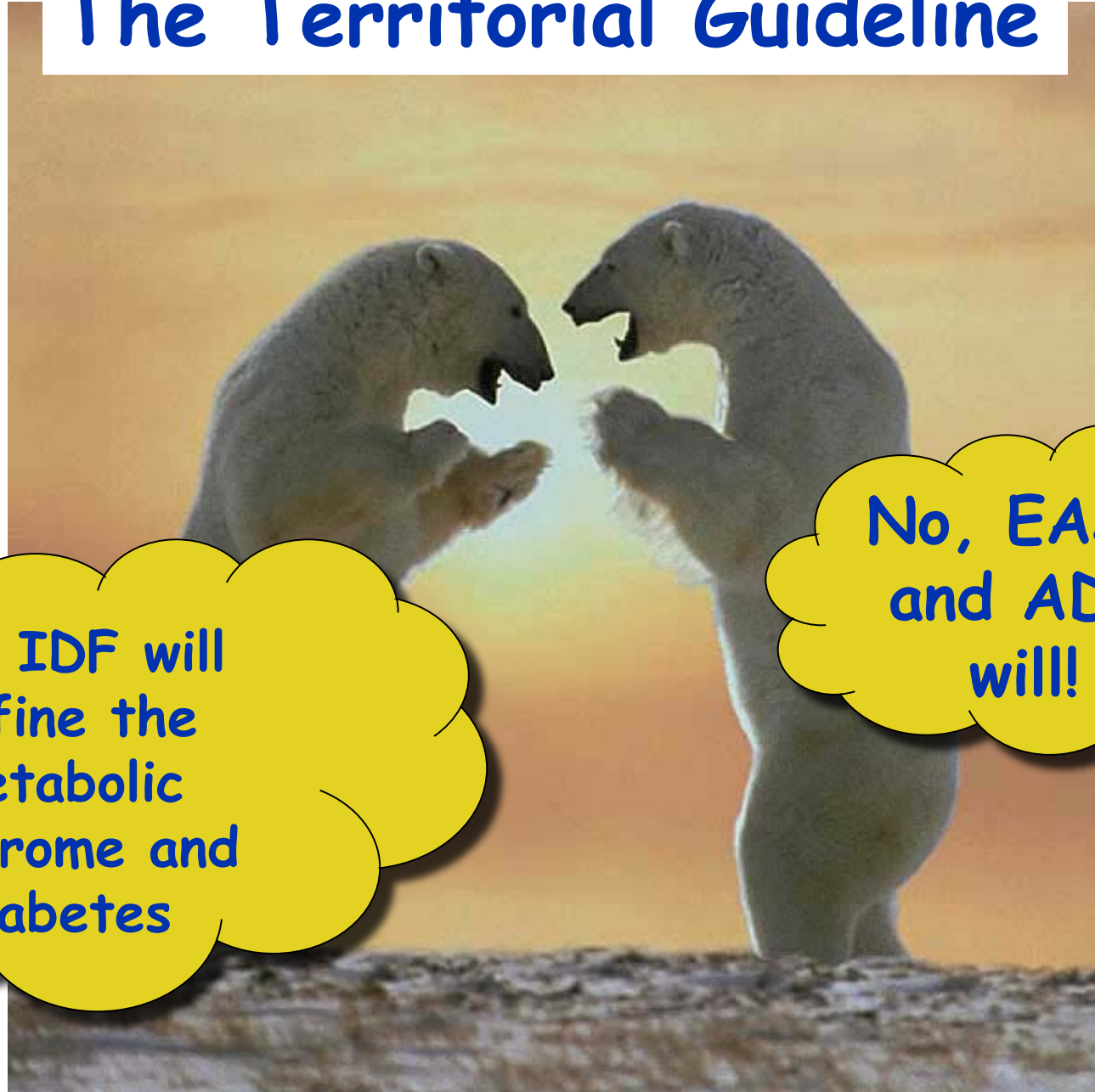
"We issue guidelines, therefore
we are important"

Any professional organisation

The Territorial Guideline



The Territorial Guideline



The IDF will
define the
metabolic
syndrome and
diabetes

No, EASD
and ADA
will!

The Imperial Guideline:



Reclassifies previously unconsidered biological variation as disease.

Guidelines Extend Disease

Examples:

Hypertension:

"Prehypertension"

Diabetes:

"Prediabetes"

Cardiology:

The NSTEMI

Hepatology:

Fatty liver to NAFLD

But the prize goes to:

Guidelines Extend Disease

Examples:

Hypertension:

"Prehypertension"

Diabetes:

"Prediabetes"

Cardiology:

The NSTEMI

Hepatology:

Fatty liver to NAFLD

But the prize goes to:

Nephrology: Reduced GFR of ageing becomes CKD!

“All individuals with a Glomerular filtration rate (GFR) <60 mL/min/1.73 m² for 3 months are classified as having chronic kidney disease, **irrespective of the presence or absence of kidney damage..**



**Guidelines do not set out to reduce the
boundaries of disease**

They set out to increase it

The Pathology of Guidelines

1. Guidelines that have a political agenda
2. Guidelines that claim to be evidence based
3. Guidelines that aspire to the point of therapeutic futility

“The concept of ‘evidence-based medicine’ has been originally formulated in the English language and it rapidly appeared that the word ‘evidence’ as used by Sackett et al was not easy to be adequately translated in other languages”.

Pierre Lefebvre

Evidence-based medicine works well for situations involving well-defined patient groups, binary alternatives, and well defined outcomes...

...But consider management of type 2 diabetes.
Our decision pathway must incorporate patients at
different stages of the disease process, with
varying pathophysiology and varying clinical
manifestations of the diabetes syndrome...

...We will construct our decision pathway from information acquired in an unsystematic way from multiple sources, from different populations, in different formats, at different times, and in different situations...

...We will conflate trial-based evidence with epidemiological observation and mechanistic considerations, and we will allow for the simultaneous application of multiple therapies which have not been tested against one another in well-conducted clinical trials, and whose safety may be uncertain...

... And we will then be able to estimate the impact of our management upon quality of life, cost, and a range of clinical outcomes.

Consensus

“When people can't agree about something, they reach a consensus”

Margaret Thatcher

“A consensus means that everyone agrees to say collectively what no one believes individually”

Abba Eban

The Pathology of Guidelines

1. Guidelines that have a political agenda
2. Guidelines that claim to be evidence based
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The Therapeutic Imperative



By extending the boundaries of disease, guidelines also extend the boundaries of treatment...

Guidelines try to define
the ideal therapy rather
than the optimal
therapy



Problems of therapy
>risks of disease

Risks of disease
>risks of therapy



Therapeutic optimum

Physicians overestimate the benefit of interventions upon survival

		UKPDS	Physicians
Case 1	Before	5.1	6.9 yrs
	After	5.9	11.5 yrs
Case 2	Before	9.3	11.8 yrs
	After	9.4	19 yrs
Case 3	Before	10.7	9.8 yrs
	After	10.9	17 yrs

**Guidelines generally
ignore adverse
events**



**Problems of therapy
>risks of disease**

**Risks of disease
>risks of therapy**

Therapeutic optimum

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Type 1 and type 2 diabetologists

Least worst diabetes management?

“When one admits that nothing is certain, one must, I think, also add that some things are much more nearly certain than others”

Bertrand Russell

A red, cloud-like shape with a drop shadow, containing the text 'Some more certain conclusions'.

**Some
more certain
conclusions**

- **Glucose control strongly influences the risk of microvascular complications, but the benefits diminish with age**
- **Glucose control is more valuable in primary than secondary prevention of vascular outcomes**

No vascular disease

PRIMARY
prevention



GLUCOSE

Clinically apparent
vascular disease

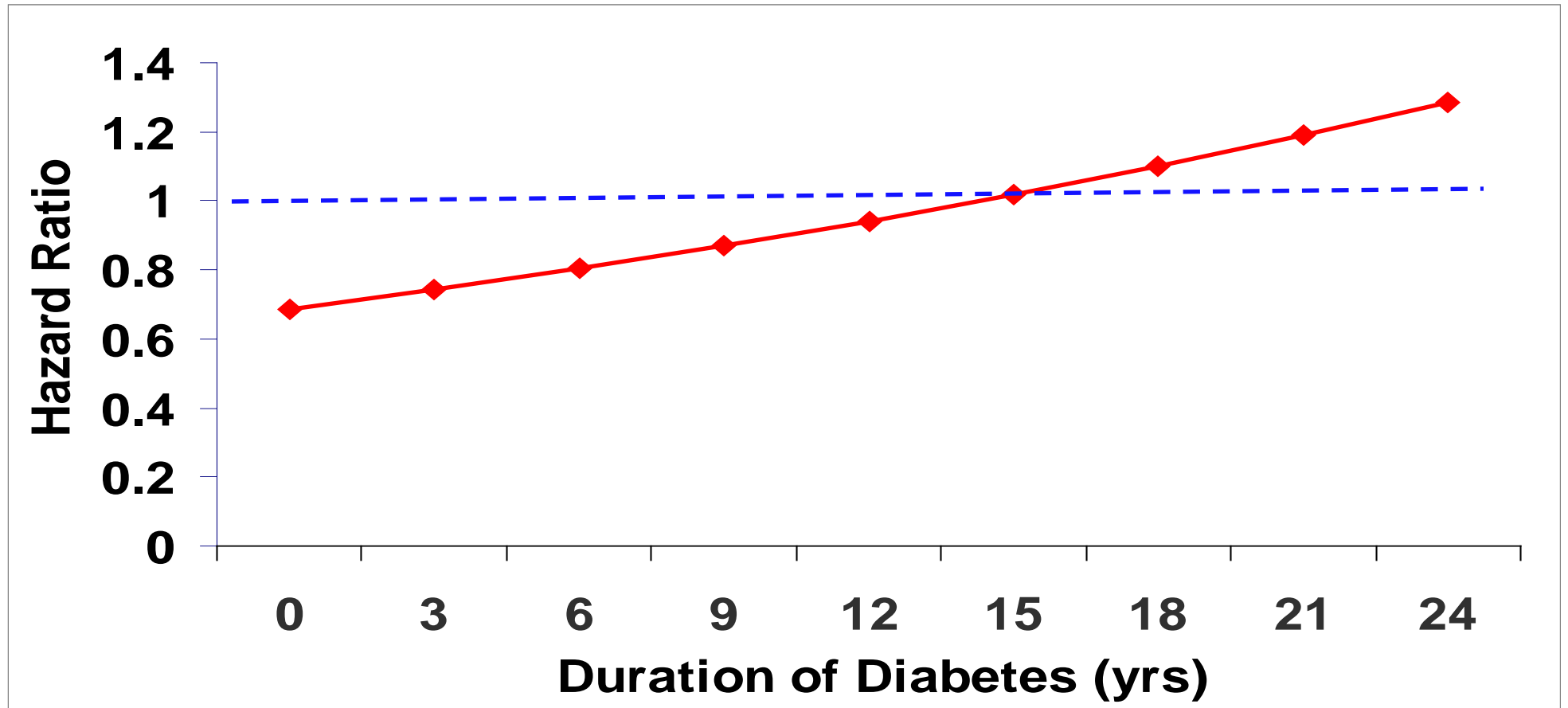
SECONDARY
prevention



BP, Lipids,
other

Disabling
vascular disease

VADT - HR for Primary Outcome in Intensive Arm



A red, cloud-like shape with a drop shadow, containing the text 'Some more certain conclusions'.

Some more certain conclusions

- Some therapies (e.g. metformin) may be more effective for CVD than others with similar glucose-lowering properties
- Glucose targets below HbA1c 8% represent a good therapeutic compromise in most older patients
- But we should treat biological age, not chronological age

A red, cloud-like shape with a drop shadow, containing the text 'Some more certain conclusions'.

**Some
more certain
conclusions**

- More therapeutic effort should be directed to those with HbA1c levels $>8\%$
- But we should acknowledge that the limitations to good glucose control are more behavioral than pharmacologic ...

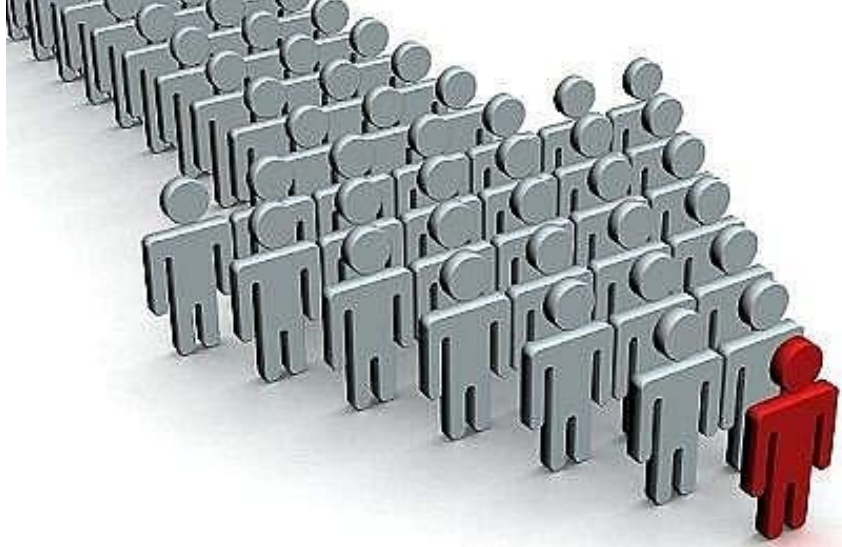


"I'm going to increase the dose of those tablets you aren't taking"

A red, cloud-like shape with a drop shadow, containing the text "Some more certain conclusions".

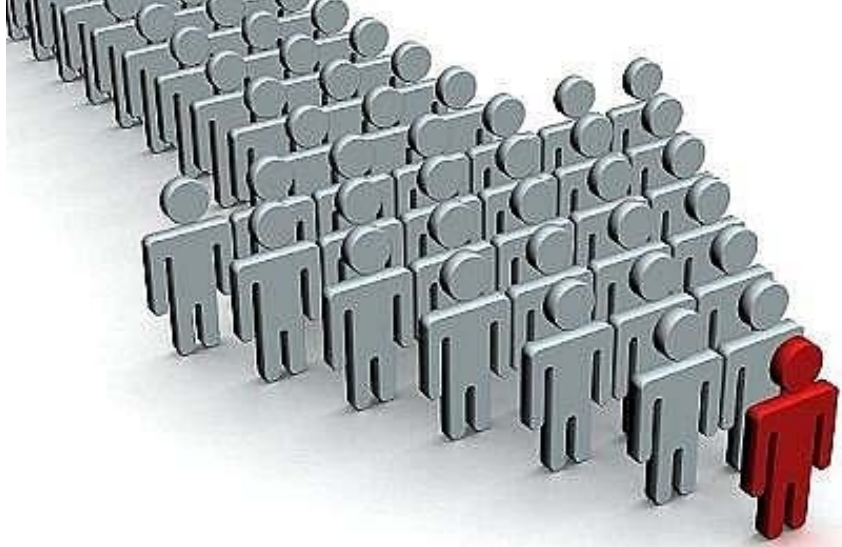
**Some
more certain
conclusions**

- “One size fits all” recommendations may be OK for populations
- But each person who comes to us is unique
- “People do not have outcomes. A person is an outcome”



There are two type of Diabetologist:

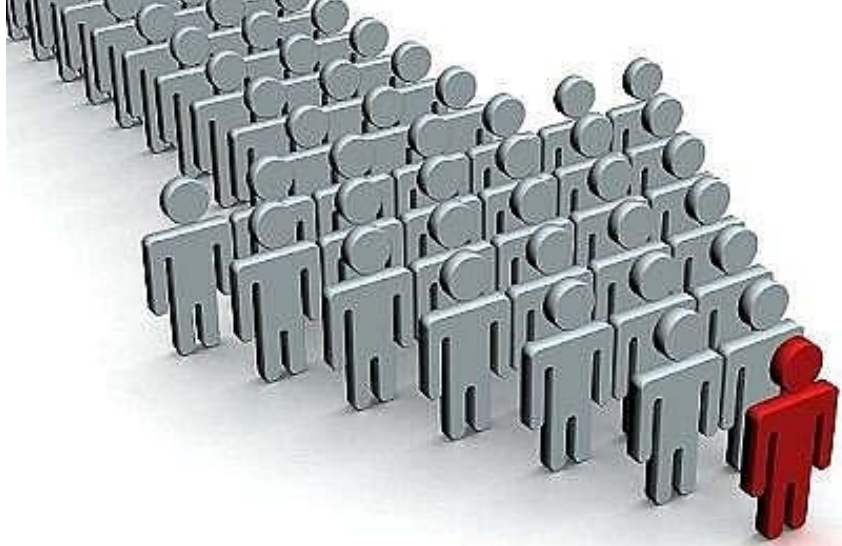
Type 1 and Type 2



There are two type of Diabetologist:

Type 1 and Type 2

Type 1 diabetologists treat diabetes



There are two type of Diabetologist:

Type 1 and Type 2

Type 1 diabetologists treat diabetes

Type 2 diabetologists treat people who have diabetes

Thank you
for listening!

