Modelling diabetes

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Chronic diseases…..

- are long-term
  - Affect quality of life, health care use, mortality over remaining lifetime
- are complex
  - Multiple risk factors
  - Multiple complications
  - Issues of competing risk
- require extended & combined treatments
  - Poor long-term evidence on disease history, treatment combinations

Hence, interest in predictive models

- Use available data to construct a disease model that…
  - predicts outcomes over a population's or patient's lifetime
  - helps generalise between studies, populations & interventions
- Such models are simplifications or approximation of the data
  - do not reflect all of reality

"All models are wrong, but some are useful."

George E.P. Box

A breast cancer example:

The Finprog Study - a Nationwide Breastcancer Database

Start Page | Survival estimation | Feedback

» Overview

» Case-matching

Profile 1:

Lymph node status	positive
Age	> 50 yrs
Tumour size	2.1-5.0 cm
Histologic type	------ All ------
Histologic grade	grade 3
ER	negative
PgR	------ All ------
erbB2 (HER-2)	------ All ------
Method of detect.	------ All ------
Adjuvant therapy	------ All ------

BOS ○

DDFS ◉

Confidence intervals ☐

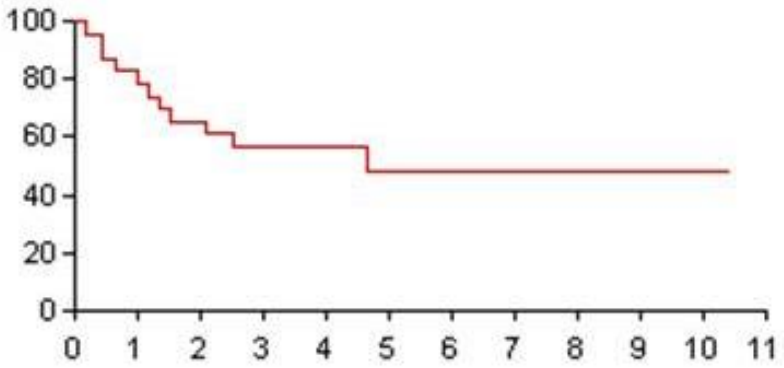
Number at risk ☐

Chart: 8 y status as a ----------

Calculate

Number of patients matching selected criteria: 23

Click to zoom graph



Years	1	3	5	8	10
Cum. Survival:	78%	57%	48%	48%	48%

Help

Which patients does the case-match system apply to?

Patients not suitable for case-matching

How to use the case-match system

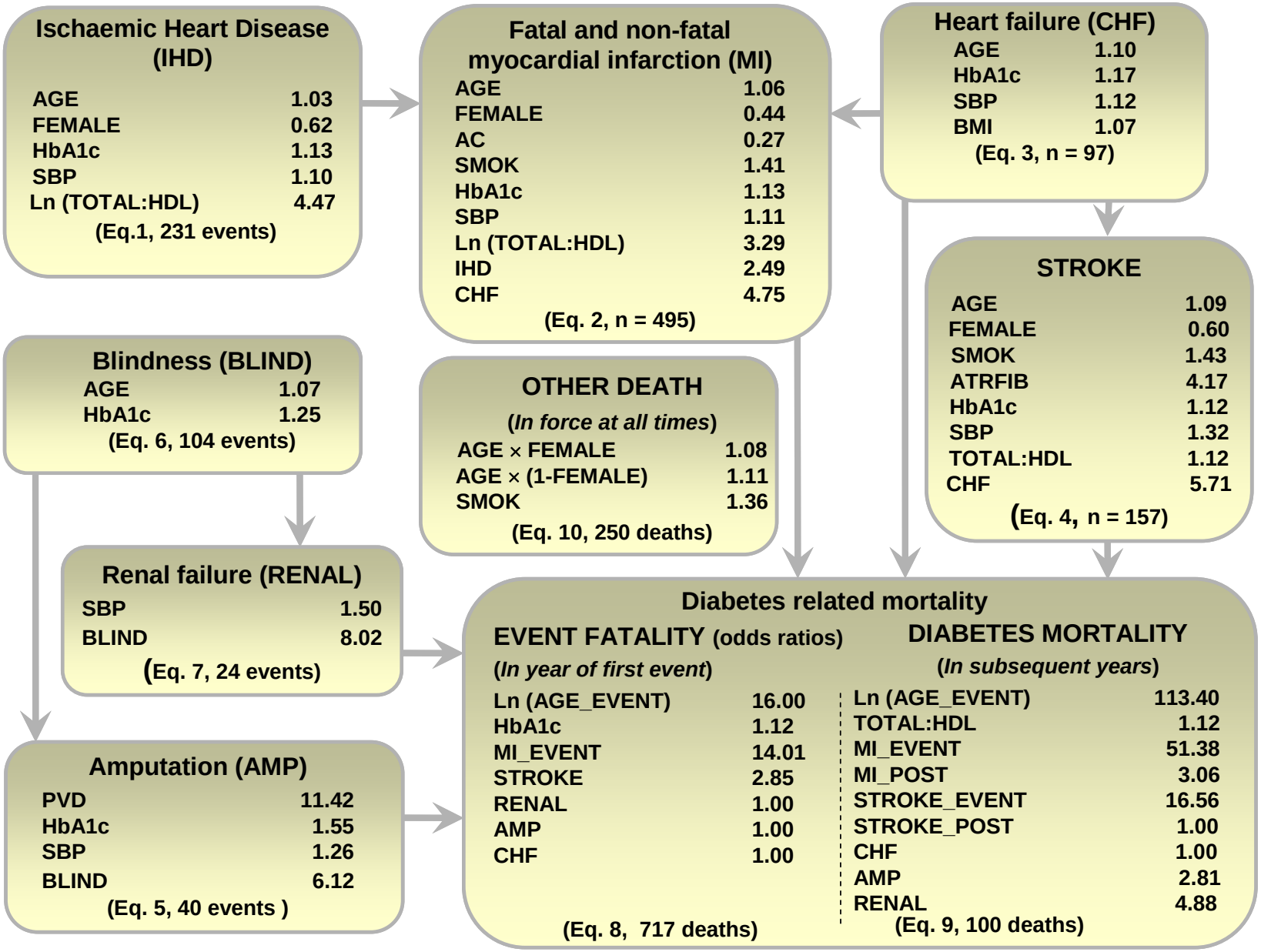
The United Kingdom Prospective Diabetes Study (UKPDS)

- A large multi-centre long term trial
  - 5,102 patients in 23 clinical centres across UK
- Compared:
    - Intensive glucose control vs conventional
    - Tight blood pressure control vs conventional
- Showed conclusively that improving blood glucose and/or blood pressure could reduce complications

The UKPDS Outcomes Model

- Uses UKPDS patient data to develop a comprehensive health outcomes model for people with type 2 diabetes
- Predicts risk of major diabetes-related complications
  - Stroke, MI, heart failure, amputation, renal failure, ischaemic heart disease (IHD) and blindness
  - Capture time varying risk factors such as HbA1c and history of previous complications
- Estimates lifetime health outcomes in terms of
  - event rates
  - life expectancy
  - quality of life
  - complication costs

UKPDS OM (V.1) model equations



Example of model process (I)

Patient at Year 1:
White male; 65 years of age (diabetes diagnosed at 60); BMI of 33; HbA1c of 7.6%; Total/HDL of 5.6%; BP 143mmHg; Smoker; No atrial fibrillation and no PVD at diagnosis; No history of diabetes-related events.

Commence model cycle 1

Random order of event equations:

CHF	P=0.010 > RD (0.005)
CHF fatality	P=0.090 < RD (0.807)
Renal failure	P=0.001 < RD (0.240)
MI	P=0.157 < RD (0.450)
IHD	P=0.003 < RD (0.030)
Stroke	P=0.056 < RD (0.890)
Amputation	P=0.005 < RD (0.010)
Blindness	P=0.008 < RD (0.657)
Other mortality	P=0.011 < RD (0.784)

Dead?

No

Patient risk factors are updated using the risk equations:

HbA1c	7.8%
Blood pressure	145
Total:HDL	5.6%
Smoking	Yes

History of diabetes-related events:

CHF

Example of model process (II)

Patient at Year 2:
White male; 66 years of age (diabetes diagnosed at 60); BMI of 33; HbA1c of 9.9%; Total/HDL of 5.5%; BP 164mmHg; Smoker; No atrial fibrillation and no PVD at diagnosis; CHF developed in Year 1.

Model cycle 2

Random order of event equations:

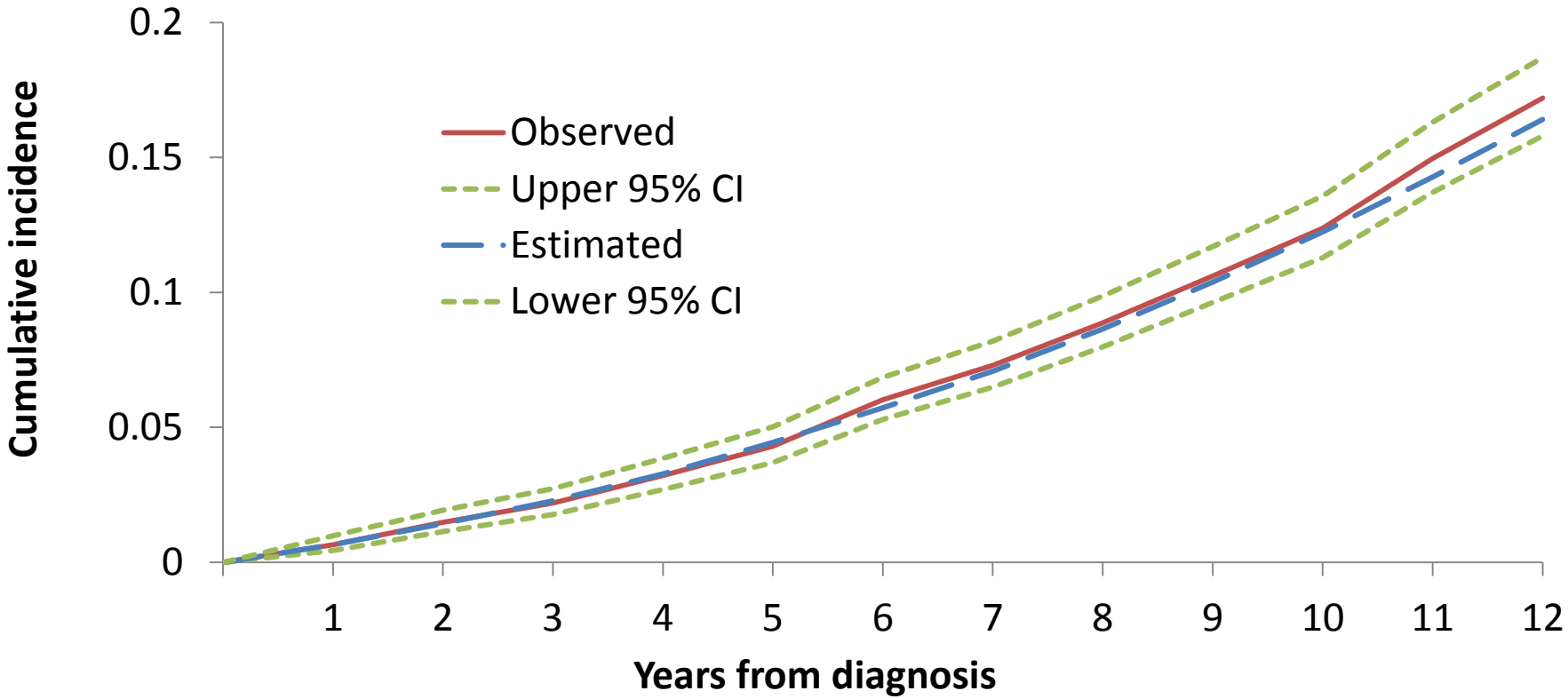
Renal failure	P=0.001 < RD (0.34)
CHF	P= 1
MI	P=0.169 > RD (0.11)
IHD	P=0.004 < RD (0.20)
Stroke	P=0.065 < RD (0.98)
Diabetes-related mortality	P=0.601 > RD (0.34)
Other mortality	NR (P=0.013)
Blindness	NR (P=0.007)
Amputation	NR (P=0.004)

Dead?

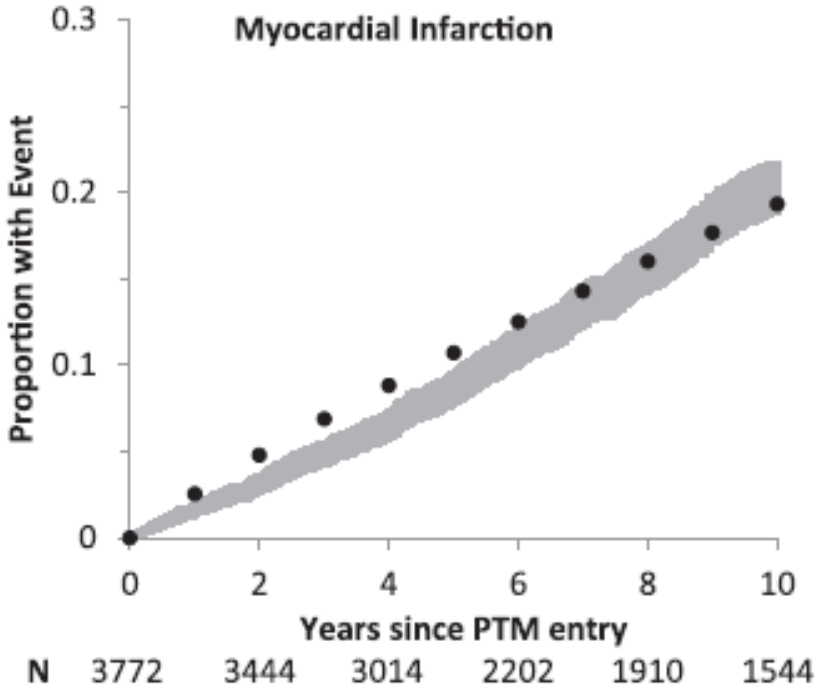
Yes

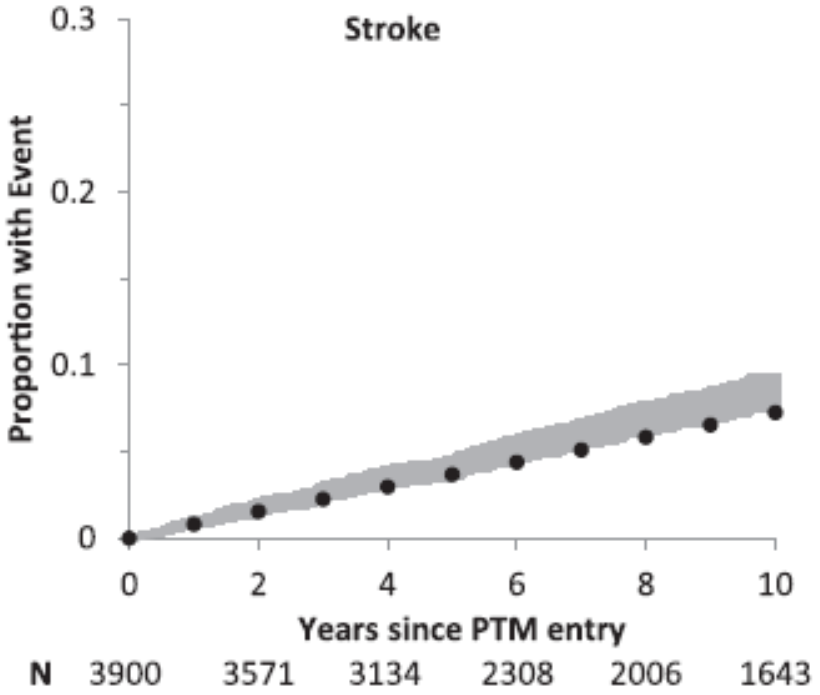
Calculation of benefit measures:
Life years: 1 + 0.5 = 1.5
QALYs: 0.677 + 0.311 = 0.988

Internal validation (Death):



Temporal validation:





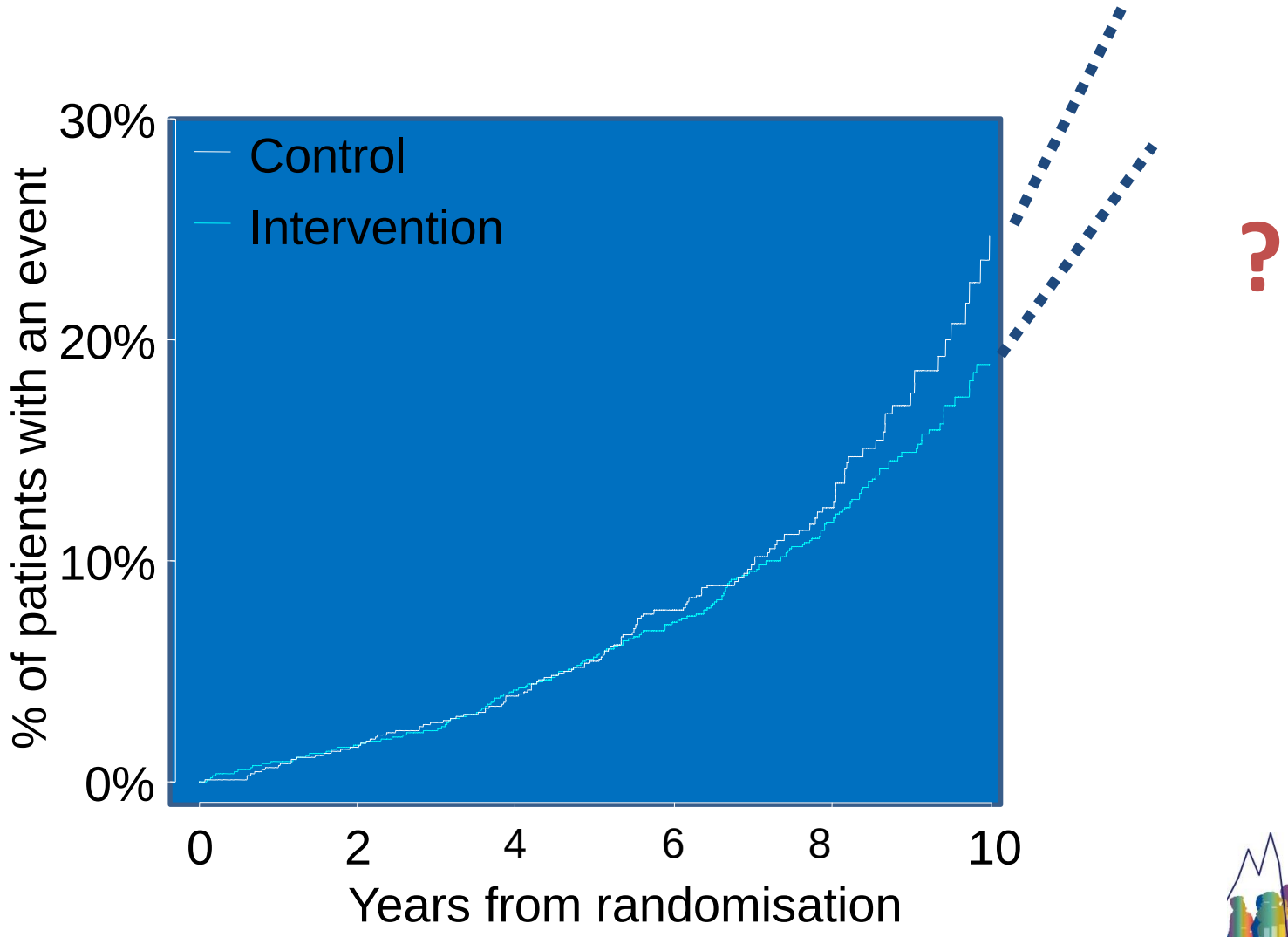
External validation:

- 4-year coronary event rates reported by CARDS* & estimated by several models

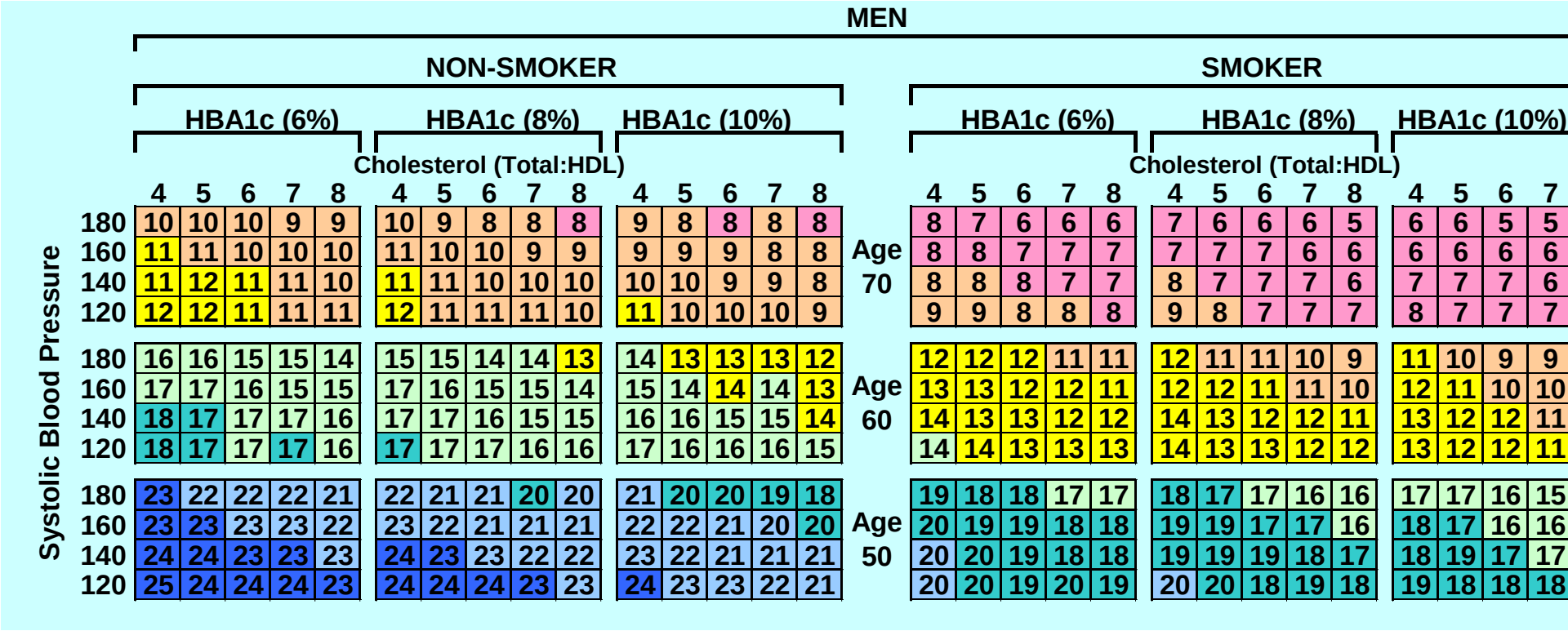
	Control	Intervention
CARDS - ACTUAL	5.5	3.6
PREDICTED:		
CDC/RTI	6.4	4.3
EAGLE	3.9	-
CARDIFF	6.7	4.5
SHEFFIELD	7.8	5.7
UKPDS OUTCOMES MODEL	5.3	3.6
UKPDS RISK ENGINE	8.0	5.2
CORE	6.4	4.5
ARCHIMEDES	5.4	3.4

Mount Hood 4 Modeling Group. Computer modeling of diabetes mellitus and its complications: a report on the fourth mount hood challenge meeting. *Diabetes Care* 2007; *30 :*1638-1646.

Using the model: Extrapolation



A Type 2 diabetes life expectancy table: MEN



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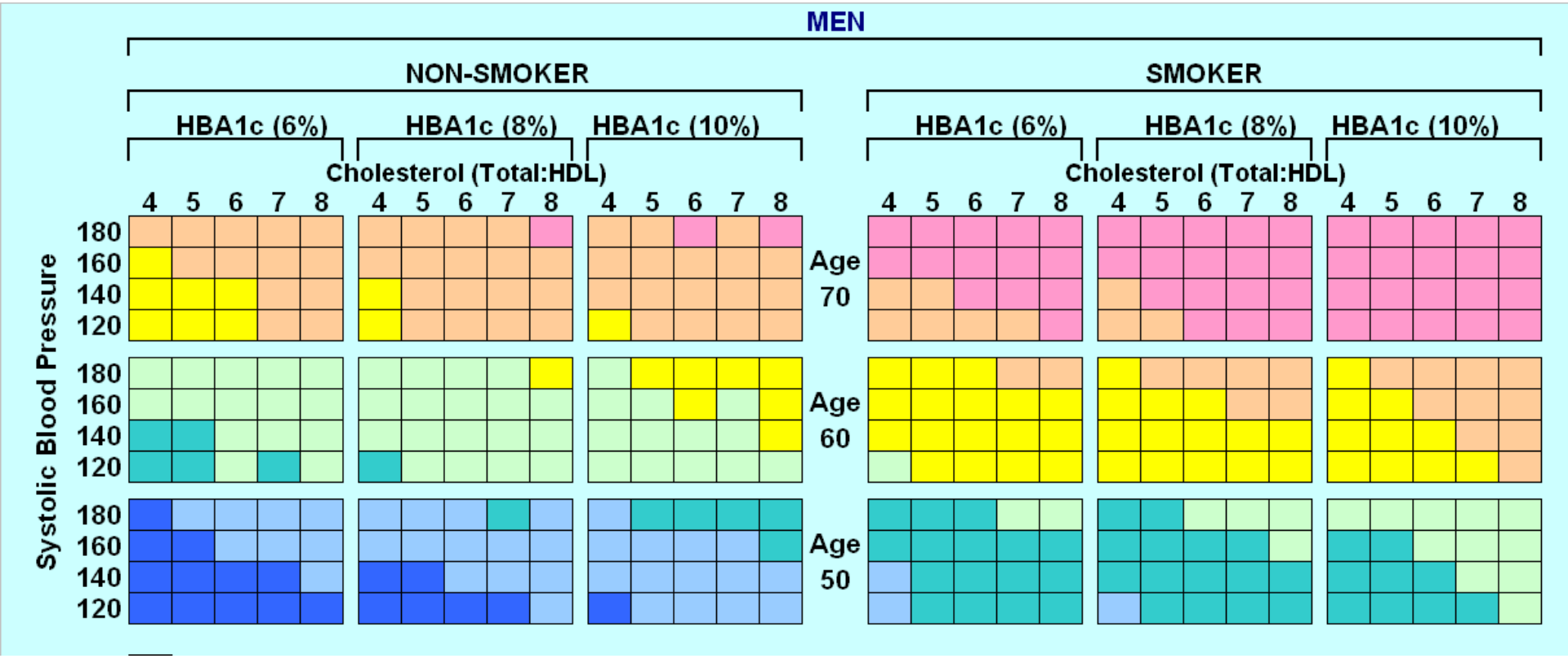

- <8 YEARS
- 8-10 YEARS
- 11-13 YEARS
- 14-16 YEARS
- 17-19 YEARS
- 20-22 YEARS
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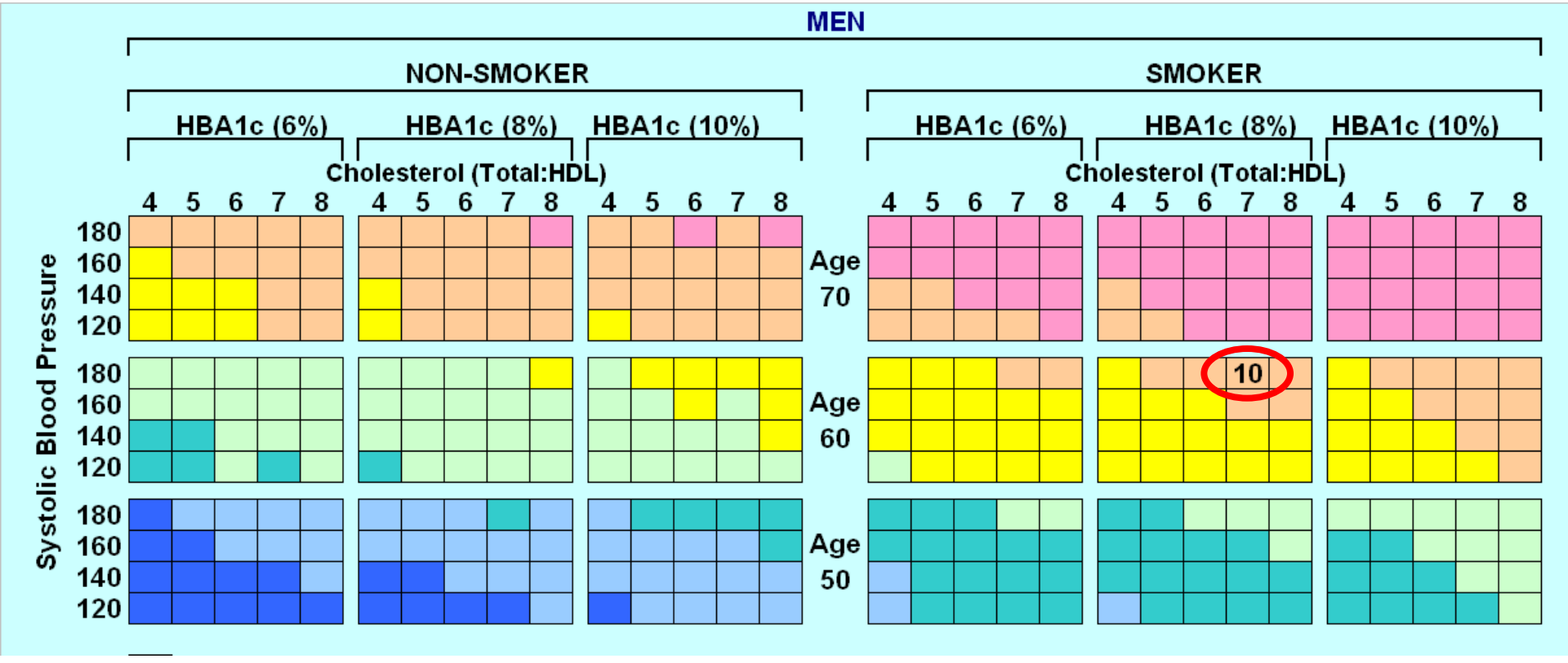

Patient: a 60 year old hypertensive smoker

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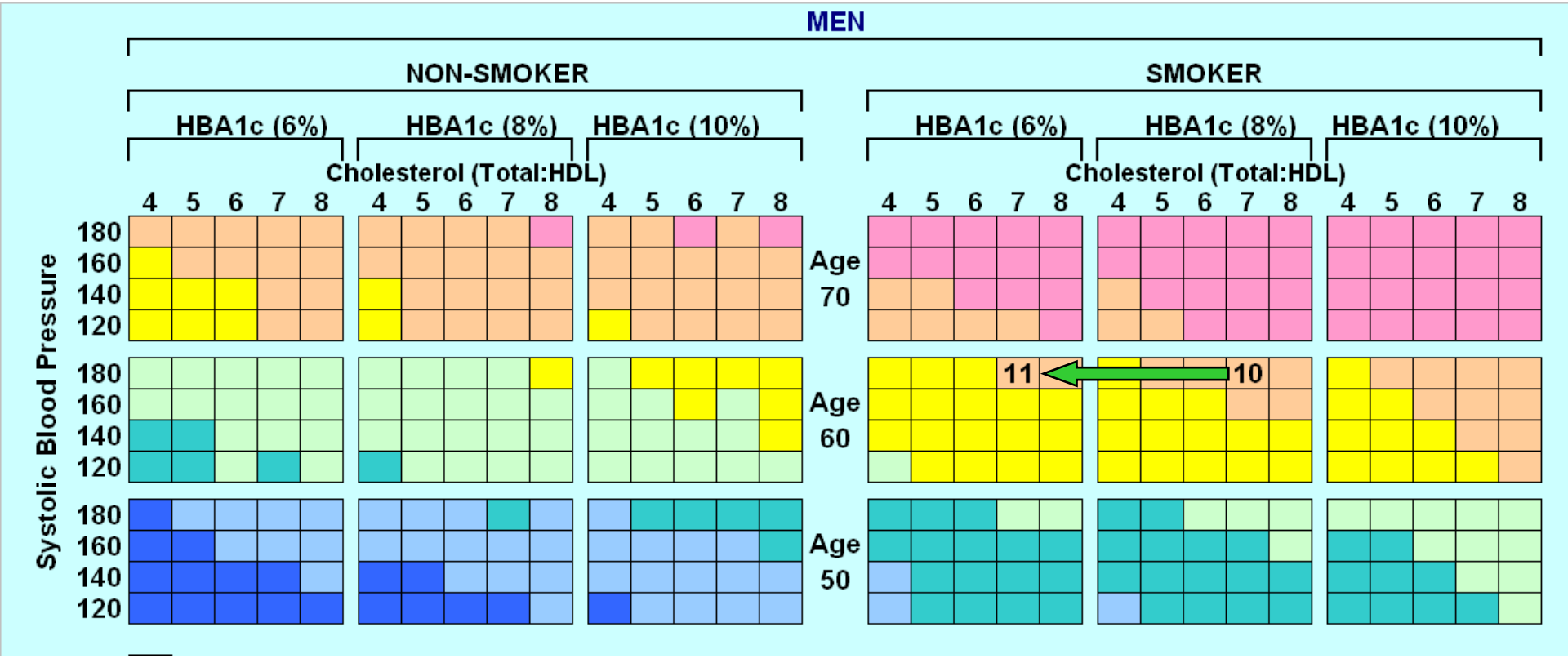

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: reduce HBA1c from 8% to 6% = + 0.7 year

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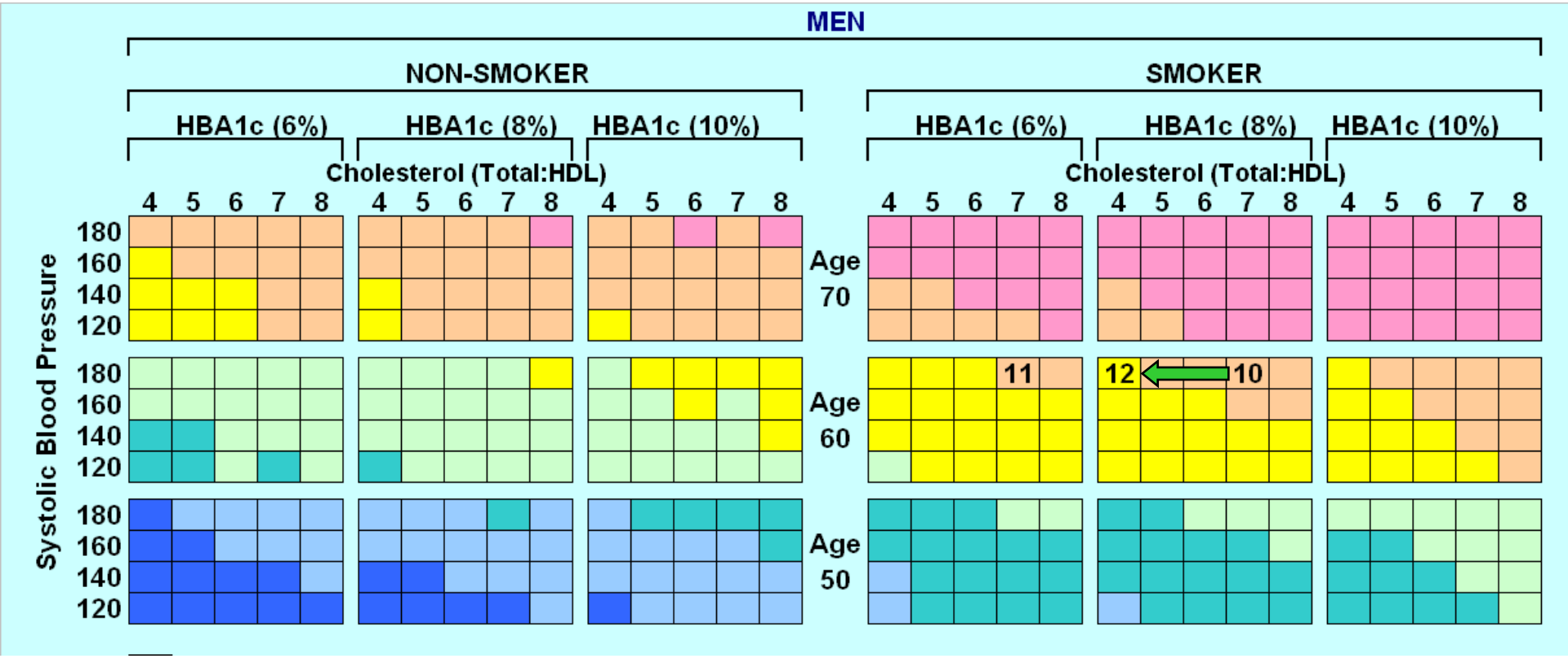

Patient: a 60 year old hypertensive smoker

: reduce HBA1c from 8% to 6% = + 0.7 year

: reduce Total/HDL cholesterol 7 to 4 = + 1.9 years

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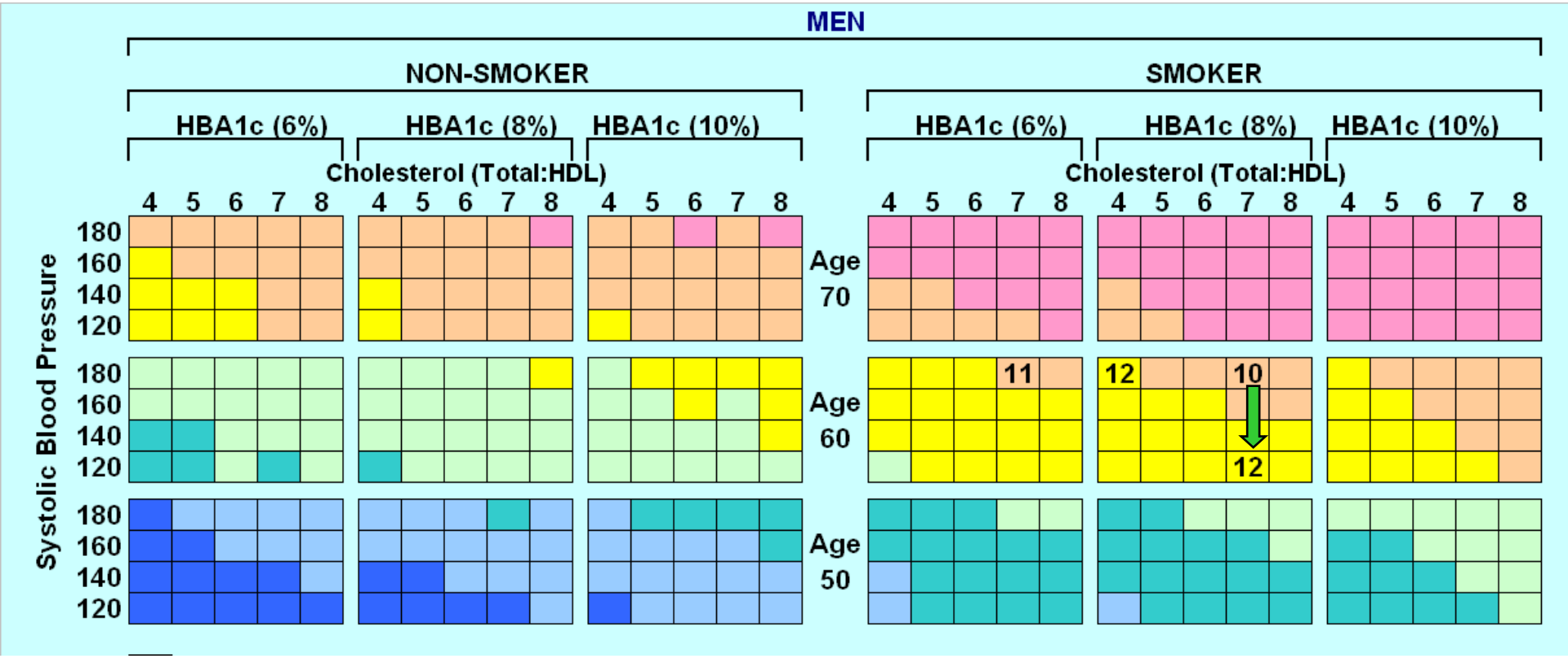

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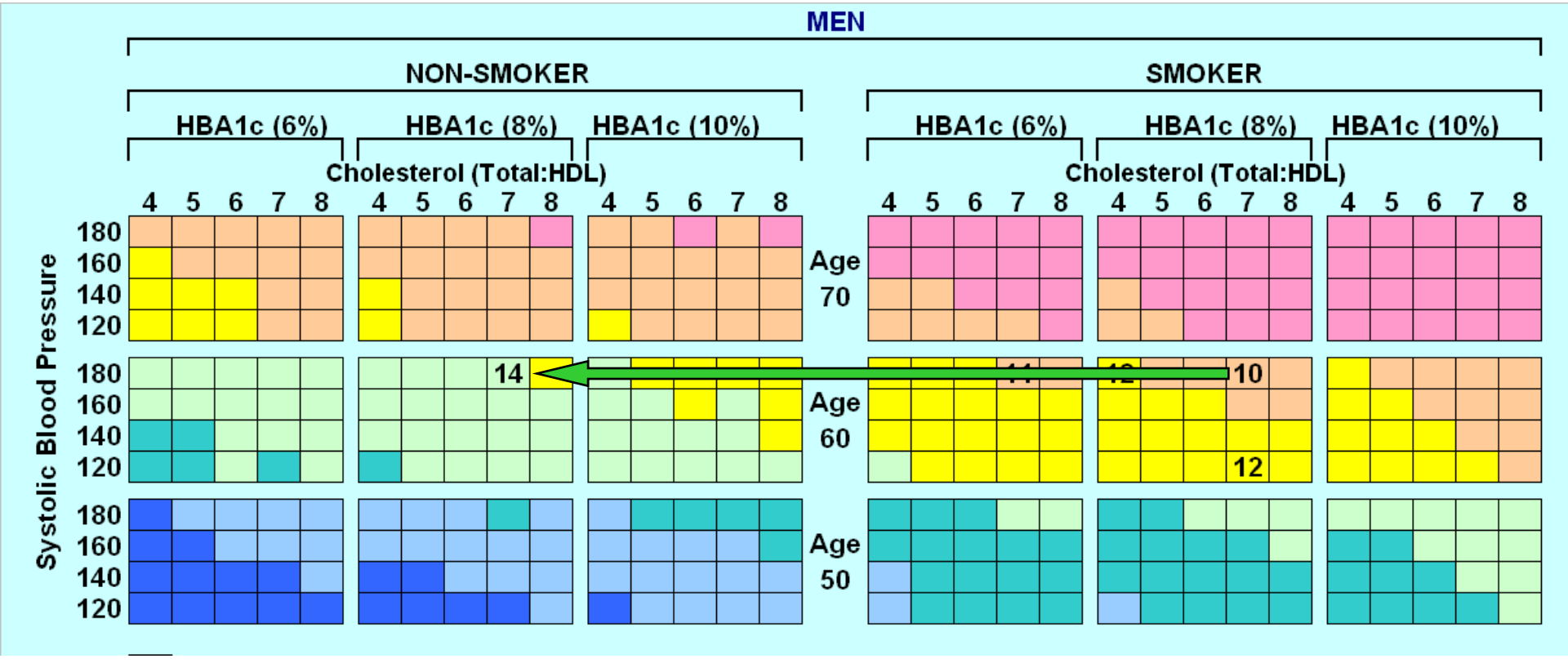

Patient: a 60 year old hypertensive smoker

: reduce HBA1c from 8% to 6%	=	+ 0.7 year
: reduce Total/HDL cholesterol 7 to 4	=	+ 1.9 years
: reduce SBP 180 to 120	=	+ 2.0 years
: stop smoking	=	+ 3.9 years

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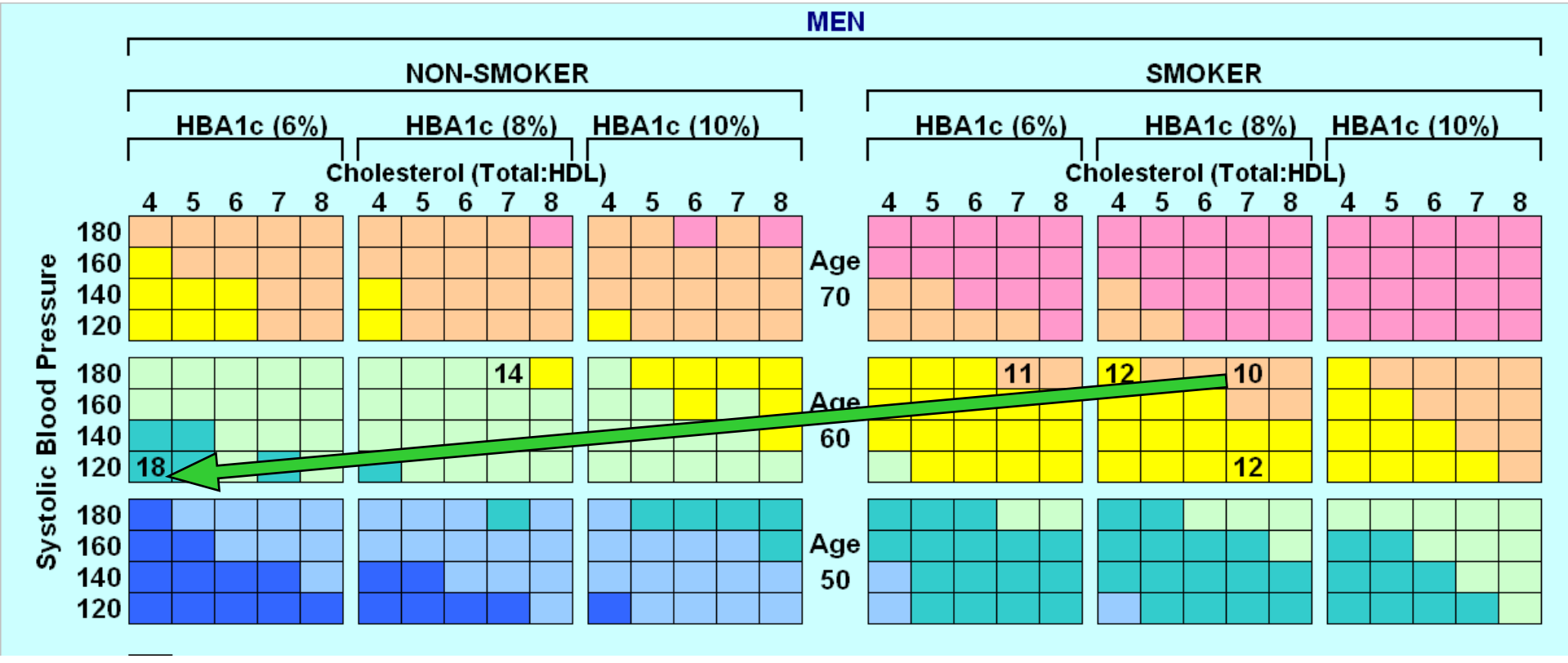

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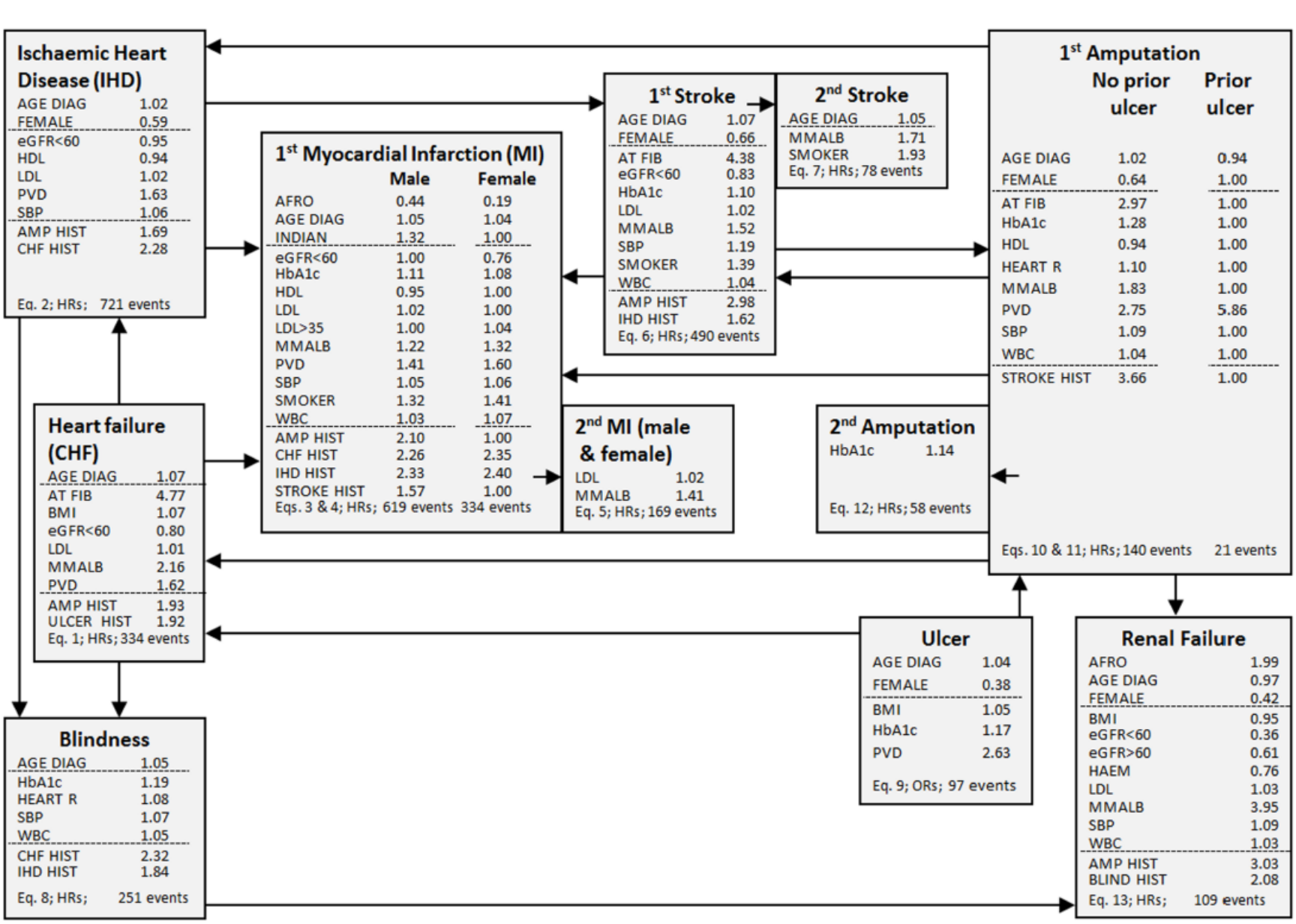
: reduce Total/HDL cholesterol 7 to 4	=	+ 1.9 years
: reduce SBP 180 to 120	=	+ 2.0 years
: stop smoking	=	+ 3.9 years
: do all above	=	+ 7.4 years

Version 2 now released, using added follow-up data



Licensing the UKPDS Outcomes Model

- All model equations published & freely available
- All quality of life/cost data published & freely available
- An approved software version of the model has been developed and commercialized
  - Built in C++ with an Excel interface
  - Available through Oxford University Innovation Limited
- Free to academic, charitable, public sector users
- Negotiated fee for commercial use

Licensing the UKPDS Outcomes Model

	Non-commercial	Commercial
Version 1.0/1.1 Aug 2005 - June 2007	36	2
Version 1.2 June 2007 - May 2009	21	13
Version 1.2.1 May 2009 - Jan 2011	26	8
Version 1.3 Jan 2011 - May 2015	97	6
Version 2.0 May 2015 - now	37	2

Commercial revenue to Oxford Innovation:

£665k

Licensing the UKPDS Outcomes Model

UK, Denmark, Germany, France, Netherlands, Spain, Belgium, Italy, Ireland, Sweden, Czech Republic, Poland, Austria

Canada, Australia, USA, New Zealand, Israel

Korea, Singapore, Japan, Hong Kong, South Africa, China, Malaysia, Chile, Mexico

Merck
GSK
Eli Lilly
Amylin
Novo Nordisk
Pfizer
Schering Plough
I3 Innovus
UBC
Boehringer Ingelheim

NICE
Veterans Administration
Canadian Agency for Drugs & Technologies in Health (CADTH)

Conclusions

- UKPDS OM is a good example of academic - industry partnership
  - Maintains highest academic standards/openness
  - Uses revenue stream for further development

- “Whether models are applicable for any given purpose must of course be investigated. This also means that a model is never accepted finally, only on trial.”

Georg Rasch