

Practical aspects of prediction in multistate models

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ARTICLE

Years of life gained by multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: 21 years follow-up on the Steno-2 randomised trial

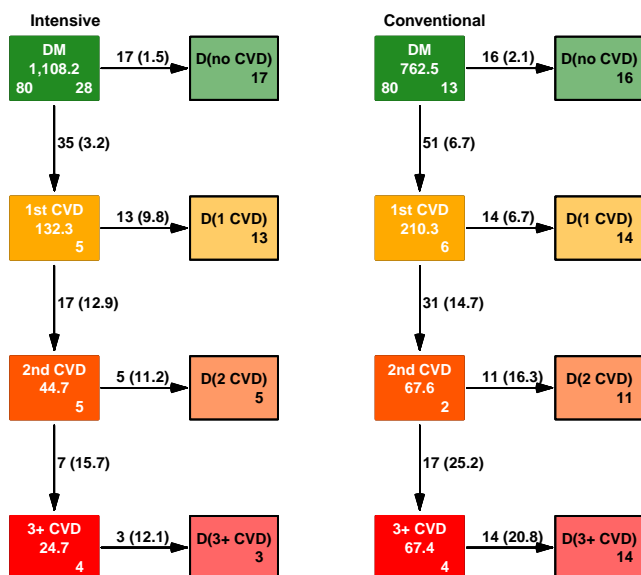
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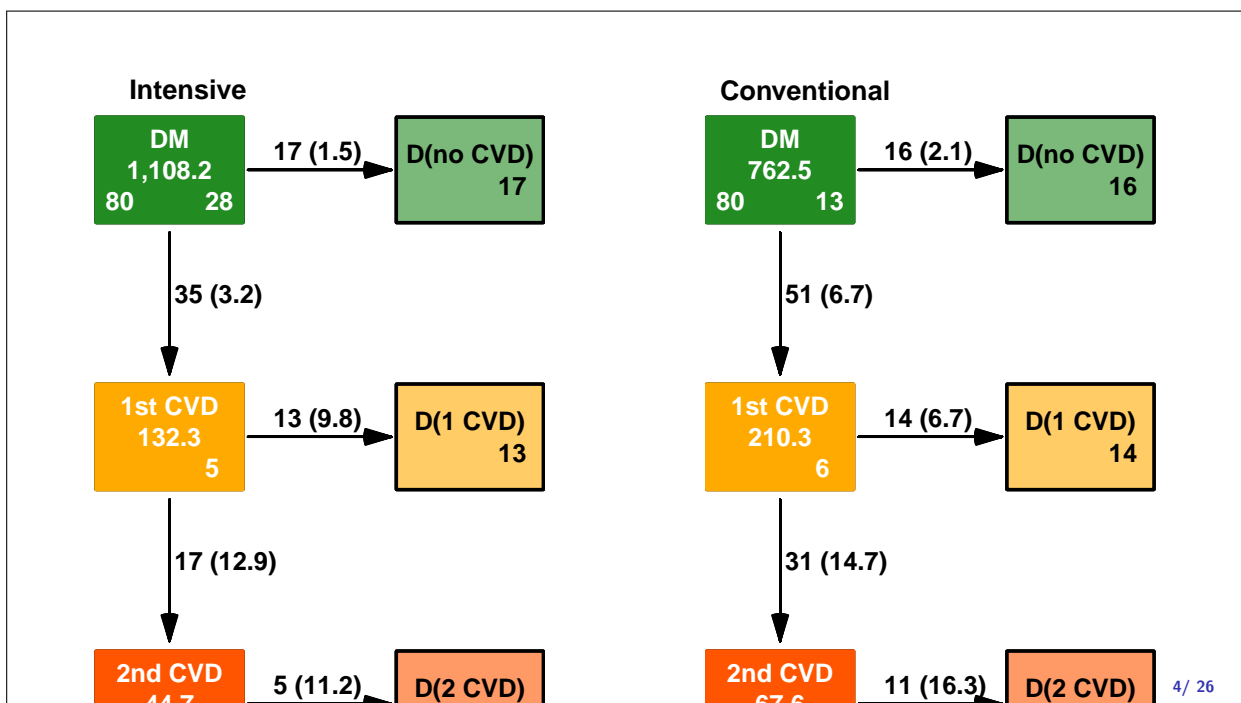
Abstract

Aims/hypothesis The aim of this work was to study the potential long-term impact of a 7.8 years intensified multifactorial

pharmacological approaches. After 7.8 years the study continued as an observational follow-up with all patients receiving treatment as for the original intensive therapy group. The pri



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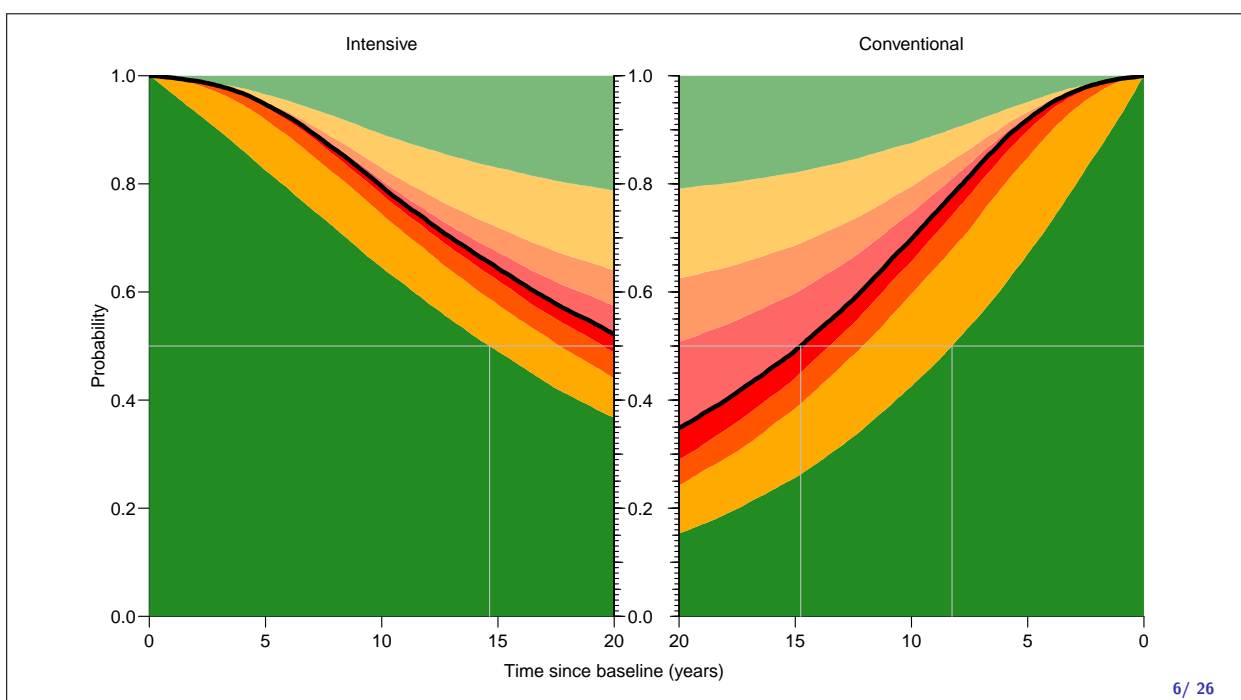


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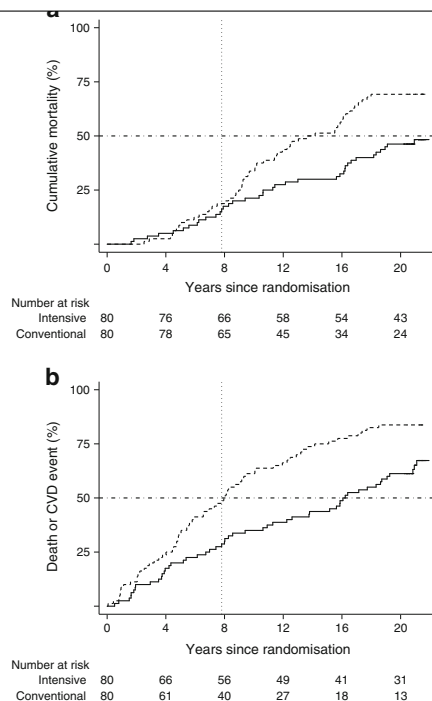
Hazard ratios

	Mortality	CVD event
HR, Int. vs. Conv.	0.83(0.54; 1.30)	0.55(0.39;0.77)
H ₀ : PH btw. CVD groups	p=0.438	p=0.261
H ₀ : HR = 1	p=0.425	p=0.001
HR vs. 0 CVD events:		
0 (ref.)	1.00	1.00
1	3.08(1.82; 5.19)	2.43(1.67;3.52)
2	4.42(2.36; 8.29)	3.48(2.15;5.64)
3+	7.76(4.11;14.65)	

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between groups (HR 0.83 [95% CI 0.54, 1.30], $p=0.43$). Thus, the reduced mortality was primarily due to reduced risk of CVD.

The patients in the intensive group experienced a total of 90 cardiovascular events vs 195 events in the conventional group. Nineteen intensive-group patients (24%) vs 34 conventional-group patients (43%) experienced more than one cardiovascular event. No significant between-group difference in the distribution of specific cardiovascular first-event types was observed (Table 2 and Fig. 4).

Microvascular complications Hazard rates of progression rates in microvascular complications compared with baseline status are shown Fig. 3. Sensitivity analyses showed a negligible effect of the random dates imputation.

Progression of retinopathy was decreased by 33% in the intensive-therapy group (Fig. 5). Blindness in at least one eye was reduced in the intensive-therapy group with an HR of 0.47 (95% CI 0.23, 0.98, $p=0.044$). Autonomic neuropathy was decreased by 41% in the intensive-therapy group (Fig. 5). We observed no difference between groups in the progression of peripheral neuropathy (Fig. 5). Progression to diabetic nephropathy (macroalbuminuria) was reduced by 48% in the intensive-therapy group (Fig. 5). Ten patients in the conventional-therapy groups vs five patients in the intensive-therapy group progressed to end-stage renal disease ($p=0.061$).

Discussion

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Expected lifetime and YLL (well, gained)

Expected lifetime (years) in the Steno 2 cohort during the first 20 years after baseline by treatment group and CVD status.

State	Intensive	Conventional	Int.–Conv.
Alive	15.6	14.1	1.5
No CVD	12.7	10.0	2.6
Any CVD	3.0	4.1	–1.1

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Expected lifetime (years) during the first 20 years after baseline by sex, age, treatment group and CVD status.

sex	state	age	Men			Women		
			Int.	Conv.	Int.–Conv.	Int.	Conv.	Int.–Conv.
Alive	45	18.5	17.5	1.0	19.1	18.4	0.7	
	50	17.2	16.1	1.1	18.0	17.2	0.8	
	55	15.6	13.8	1.8	17.4	15.9	1.6	
	60	13.9	11.6	2.2	15.5	13.7	1.8	
	65	11.2	9.5	1.8	13.3	11.4	2.0	
No CVD	45	14.9	12.5	2.4	15.8	14.3	1.5	
	50	14.0	11.1	2.9	15.1	12.9	2.2	
	55	12.2	9.7	2.5	14.3	11.6	2.7	
	60	10.9	8.2	2.7	12.4	9.9	2.6	
	65	9.0	6.7	2.2	10.7	8.3	2.4	

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Multistate models in practice:

- ▶ Representation:
 - ▶ States
 - ▶ Transitions
 - ▶ Sojourn times
 - ▶ Rates
- ▶ Analysis of rates:
 - ▶ Cox-model
 - ▶ Poisson model
- ▶ Reporting
 - ▶ Rates
 - ▶ HRs
 - ▶ Probabilities
 - ▶ Expected lifetime

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Representation of multistate FU: Lexis

- ▶ Allowing multiple time scales
 - ▶ time-scale variables — the starting point on each time scale
 - ▶ sojourn time variable `lex.dur` — risktime, exposure
 - ▶ state variables:
- ▶ Allowing multiple states
 - ▶ `lex.Cst` — the state in which follow-up (`lex.dur`) occurs
 - ▶ `lex.Xst` — the state in which

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Representation of multistate FU: Lexis I

lex.id	per	age	dur	tsb	lex.dur	lex.Cst	lex.Xst	allocation	sex
5	1993.162	57.169	6.816	0.000	0.083	DM	DM	Conventional	M
5	1993.246	57.252	6.899	0.083	0.083	DM	DM	Conventional	M
5	1993.329	57.336	6.983	0.167	0.083	DM	DM	Conventional	M
5	1993.412	57.419	7.066	0.250	0.083	DM	DM	Conventional	M
5	1993.496	57.502	7.149	0.333	0.083	DM	DM	Conventional	M
5	1993.579	57.586	7.233	0.417	0.083	DM	DM	Conventional	M
5	1993.662	57.669	7.316	0.500	0.083	DM	DM	Conventional	M
5	1993.746	57.752	7.399	0.583	0.083	DM	DM	Conventional	M
5	1993.829	57.836	7.483	0.667	0.083	DM	DM	Conventional	M
5	1993.912	57.919	7.566	0.750	0.047	DM	1st CVD	Conventional	M
5	1993.959	57.966	7.613	0.797	0.037	1st CVD	1st CVD	Conventional	M
5	1993.996	58.002	7.649	0.833	0.083	1st CVD	1st CVD	Conventional	M
5	1994.079	58.086	7.733	0.917	0.083	1st CVD	1st CVD	Conventional	M
5	1994.162	58.169	7.816	1.000	0.083	1st CVD	1st CVD	Conventional	M
5	1994.246	58.252	7.899	1.083	0.083	1st CVD	1st CVD	Conventional	M
5	1994.329	58.336	7.983	1.167	0.083	1st CVD	1st CVD	Conventional	M

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Representation of multistate FU: Lexis II

5	1994.412	58.419	8.066	1.250	0.083	1st CVD	1st CVD	Conventional	M
5	1994.496	58.502	8.149	1.333	0.083	1st CVD	1st CVD	Conventional	M
5	1994.579	58.586	8.233	1.417	0.078	1st CVD	2nd CVD	Conventional	M
5	1994.657	58.664	8.311	1.495	0.005	2nd CVD	2nd CVD	Conventional	M
5	1994.662	58.669	8.316	1.500	0.083	2nd CVD	2nd CVD	Conventional	M
5	1994.746	58.752	8.399	1.583	0.083	2nd CVD	2nd CVD	Conventional	M
5	1994.829	58.836	8.483	1.667	0.083	2nd CVD	2nd CVD	Conventional	M
5	1994.912	58.919	8.566	1.750	0.083	2nd CVD	2nd CVD	Conventional	M
5	1994.996	59.002	8.649	1.833	0.083	2nd CVD	2nd CVD	Conventional	M
5	1995.079	59.086	8.733	1.917	0.083	2nd CVD	2nd CVD	Conventional	M
5	1995.162	59.169	8.816	2.000	0.083	2nd CVD	2nd CVD	Conventional	M
5	1995.246	59.252	8.899	2.083	0.083	2nd CVD	2nd CVD	Conventional	M
5	1995.329	59.336	8.983	2.167	0.083	2nd CVD	2nd CVD	Conventional	M
5	1995.412	59.419	9.066	2.250	0.083	2nd CVD	2nd CVD	Conventional	M
5	1995.496	59.502	9.149	2.333	0.083	2nd CVD	2nd CVD	Conventional	M
5	1995.579	59.586	9.233	2.417	0.083	2nd CVD	2nd CVD	Conventional	M
5	1995.662	59.669	9.316	2.500	0.083	2nd CVD	2nd CVD	Conventional	M
5	1995.746	59.752	9.399	2.583	0.083	2nd CVD	2nd CVD	Conventional	M
5	1995.829	59.836	9.483	2.667	0.083	2nd CVD	2nd CVD	Conventional	M

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Representation of multistate FU: Lexis III

5	1995.912	59.919	9.566	2.750	0.083	2nd CVD	2nd CVD	Conventional	M
5	1995.996	60.002	9.649	2.833	0.083	2nd CVD	2nd CVD	Conventional	M
5	1996.079	60.086	9.733	2.917	0.083	2nd CVD	2nd CVD	Conventional	M
5	1996.162	60.169	9.816	3.000	0.083	2nd CVD	2nd CVD	Conventional	M
5	1996.246	60.252	9.899	3.083	0.083	2nd CVD	2nd CVD	Conventional	M
5	1996.329	60.336	9.983	3.167	0.083	2nd CVD	2nd CVD	Conventional	M
5	1996.412	60.419	10.066	3.250	0.083	2nd CVD	2nd CVD	Conventional	M
5	1996.496	60.502	10.149	3.333	0.083	2nd CVD	2nd CVD	Conventional	M
5	1996.579	60.586	10.233	3.417	0.083	2nd CVD	2nd CVD	Conventional	M
5	1996.662	60.669	10.316	3.500	0.083	2nd CVD	2nd CVD	Conventional	M
5	1996.746	60.752	10.399	3.583	0.083	2nd CVD	2nd CVD	Conventional	M
5	1996.829	60.836	10.483	3.667	0.083	2nd CVD	2nd CVD	Conventional	M
5	1996.912	60.919	10.566	3.750	0.083	2nd CVD	2nd CVD	Conventional	M
5	1996.996	61.002	10.649	3.833	0.083	2nd CVD	2nd CVD	Conventional	M
5	1997.079	61.086	10.733	3.917	0.083	2nd CVD	2nd CVD	Conventional	M
5	1997.162	61.169	10.816	4.000	0.083	2nd CVD	2nd CVD	Conventional	M
5	1997.246	61.252	10.899	4.083	0.083	2nd CVD	2nd CVD	Conventional	M
5	1997.329	61.336	10.983	4.167	0.083	2nd CVD	2nd CVD	Conventional	M
5	1997.412	61.419	11.066	4.250	0.083	2nd CVD	2nd CVD	Conventional	M

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Representation of multistate FU: Lexis IV

5	1997.496	61.502	11.149	4.333	0.083	2nd CVD	2nd CVD	Conventional	M
5	1997.579	61.586	11.233	4.417	0.083	2nd CVD	2nd CVD	Conventional	M
5	1997.662	61.669	11.316	4.500	0.083	2nd CVD	2nd CVD	Conventional	M
5	1997.746	61.752	11.399	4.583	0.083	2nd CVD	2nd CVD	Conventional	M
5	1997.829	61.836	11.483	4.667	0.083	2nd CVD	2nd CVD	Conventional	M
5	1997.912	61.919	11.566	4.750	0.083	2nd CVD	2nd CVD	Conventional	M
5	1997.996	62.002	11.649	4.833	0.051	2nd CVD	D(2 CVD)	Conventional	M

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Representation of multistate FU: Lexis

lex.id	per	age	dur	tsb	lex.dur	lex.Cst	lex.Xst	allocation	sex
5	1993.162	57.169	6.816	0.000	0.083	DM	DM	Conventional	M
5	1993.246	57.252	6.899	0.083	0.083	DM	DM	Conventional	M
...									
5	1993.829	57.836	7.483	0.667	0.083	DM	DM	Conventional	M
5	1993.912	57.919	7.566	0.750	0.047	DM	1st CVD	Conventional	M
5	1993.959	57.966	7.613	0.797	0.037	1st CVD	1st CVD	Conventional	M
...									
5	1994.496	58.502	8.149	1.333	0.083	1st CVD	1st CVD	Conventional	M
5	1994.579	58.586	8.233	1.417	0.078	1st CVD	2nd CVD	Conventional	M
5	1994.657	58.664	8.311	1.495	0.005	2nd CVD	2nd CVD	Conventional	M
...									
5	1994.746	58.752	8.399	1.583	0.083	2nd CVD	2nd CVD	Conventional	M
5	1994.829	58.836	8.483	1.667	0.083	2nd CVD	2nd CVD	Conventional	M
...									
5	1997.912	61.919	11.566	4.750	0.083	2nd CVD	2nd CVD	Conventional	M
5	1997.996	62.002	11.649	4.833	0.051	2nd CVD	D(2 CVD)	Conventional	M

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Modeling mortality rates in Lexis objects

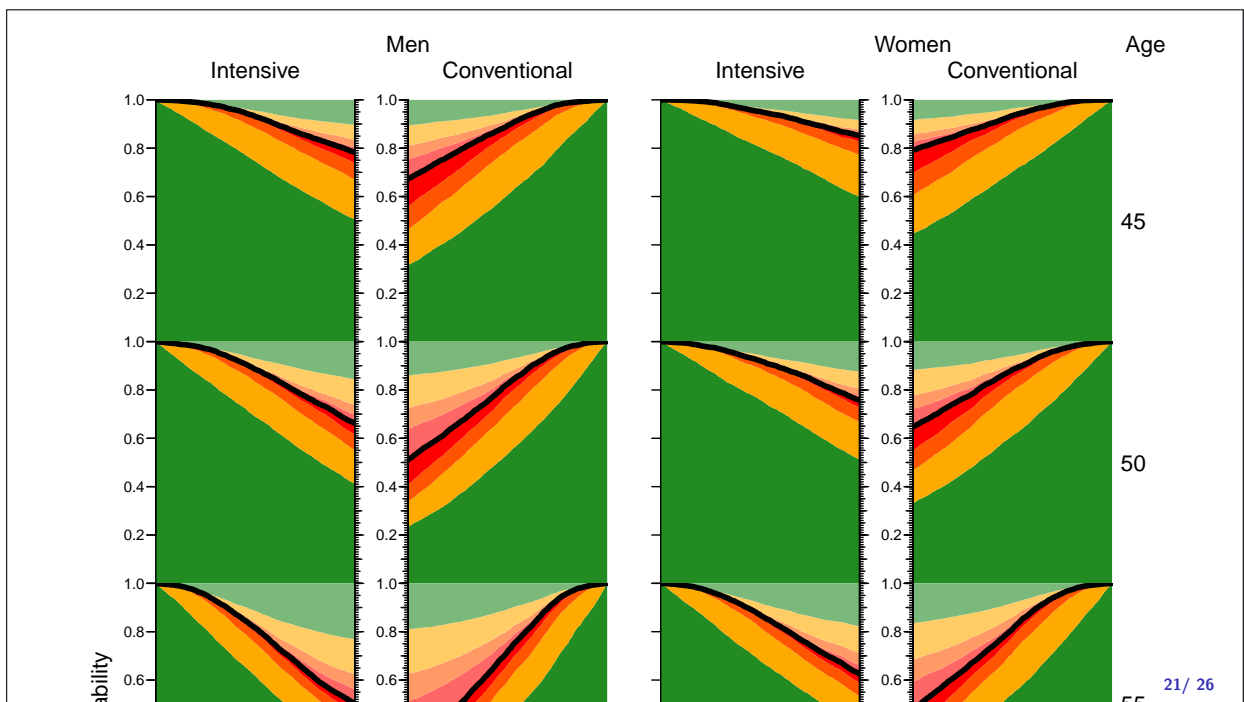
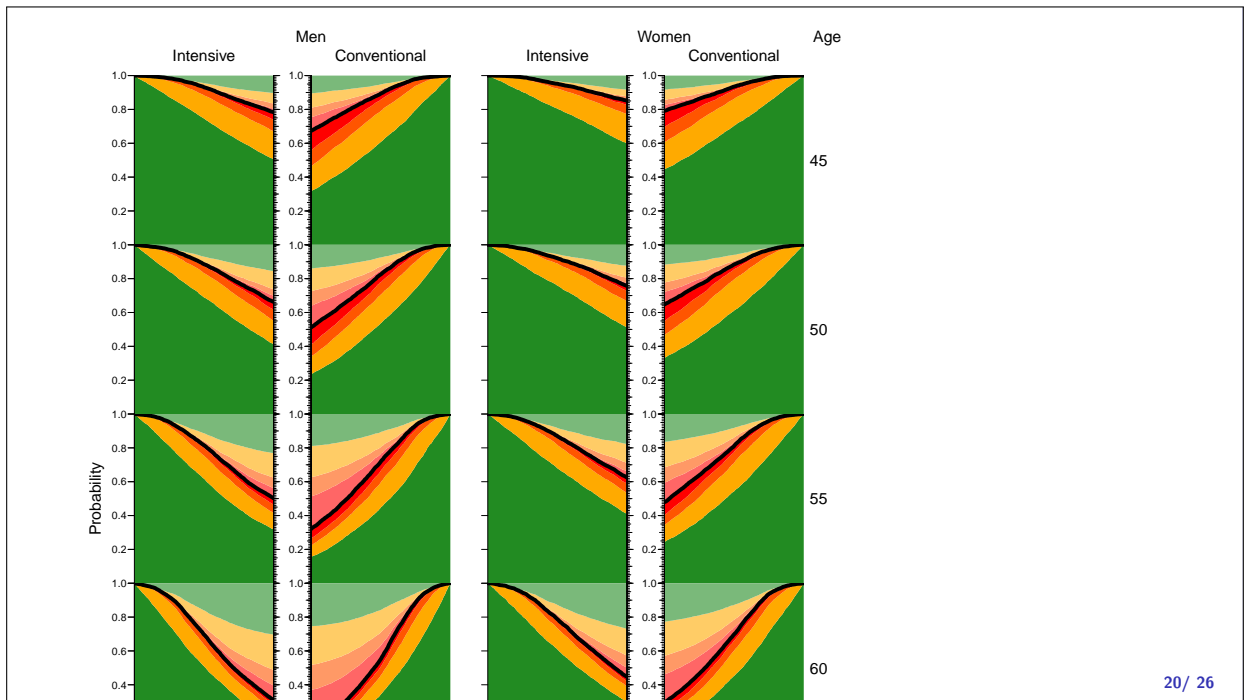
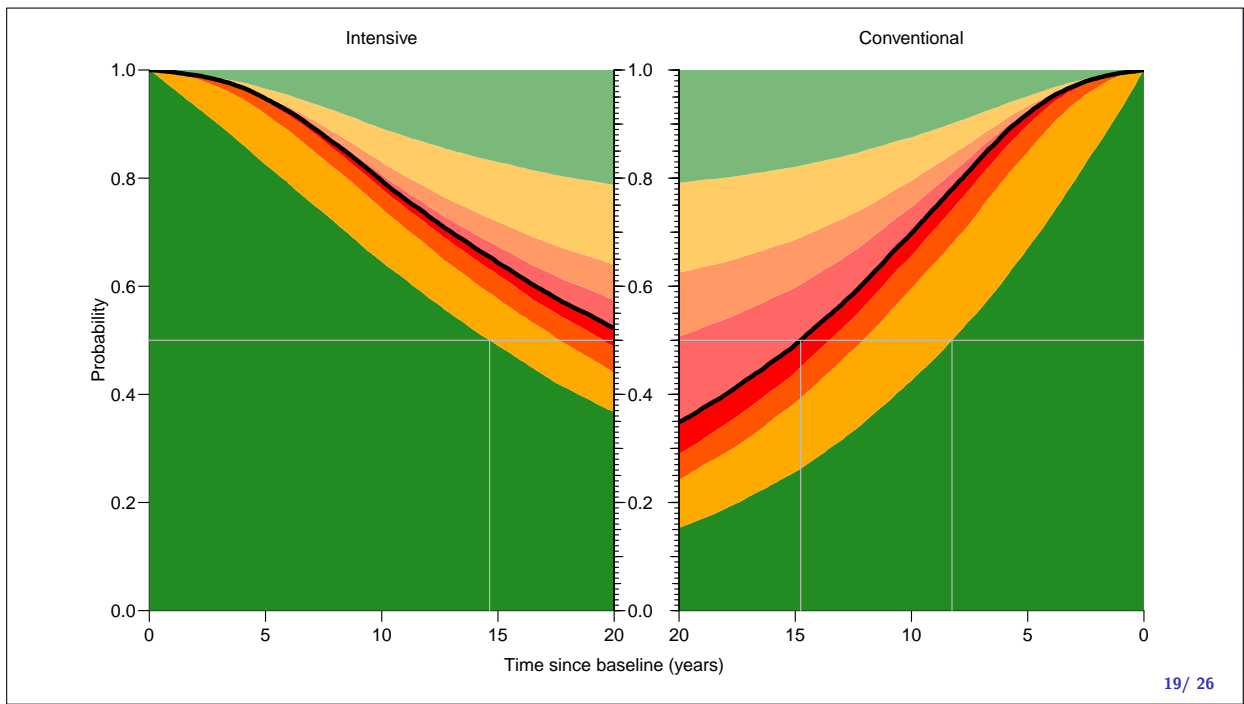
```
> dlev <- c("D(no CVD)", "D(1 CVD)", "D(2 CVD)", "D(3+ CVD)")
> #
> m0 <- glm( (lex.Xst %in% dlev) ~
+           Ns( tsb, knots=d.kn ) + lex.Cst + allocation,
+           offset = log(lex.dur),
+           family = poisson,
+           data = S1 )
> #
> m1 <- update( m0, . ~ . + sex + age ) # the real model
> #
> m1i <- update( m1, . ~ . - allocation + allocation:lex.Cst )
> #
> # Test interaction
> anova( m1i, m1, test="Chisq" )
```

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Modeling CVD rates in Lexis objects

```
> clev <- c("1st CVD", "2nd CVD", "3+ CVD")
> #
> c0 <- glm( ( (lex.Xst %in% clev) & (lex.Cst!=lex.Xst) ) ~
+           Ns( tsb, knots=d.kn ) + lex.Cst + allocation,
+           offset = log(lex.dur),
+           family = poisson,
+           data = subset( S1, lex.Cst!="3+ CVD" ) )
> #
> c1 <- update( c0, . ~ . + sex + age )
> #
> c1i <- update( c1, . ~ . - allocation + allocation:lex.Cst )
> #
> c1p <- update( c1, . ~ . + allocation:tsb )
> #
> # Test interaction & PH
> anova( c1i, c1, c1p, test="Chisq" )
```

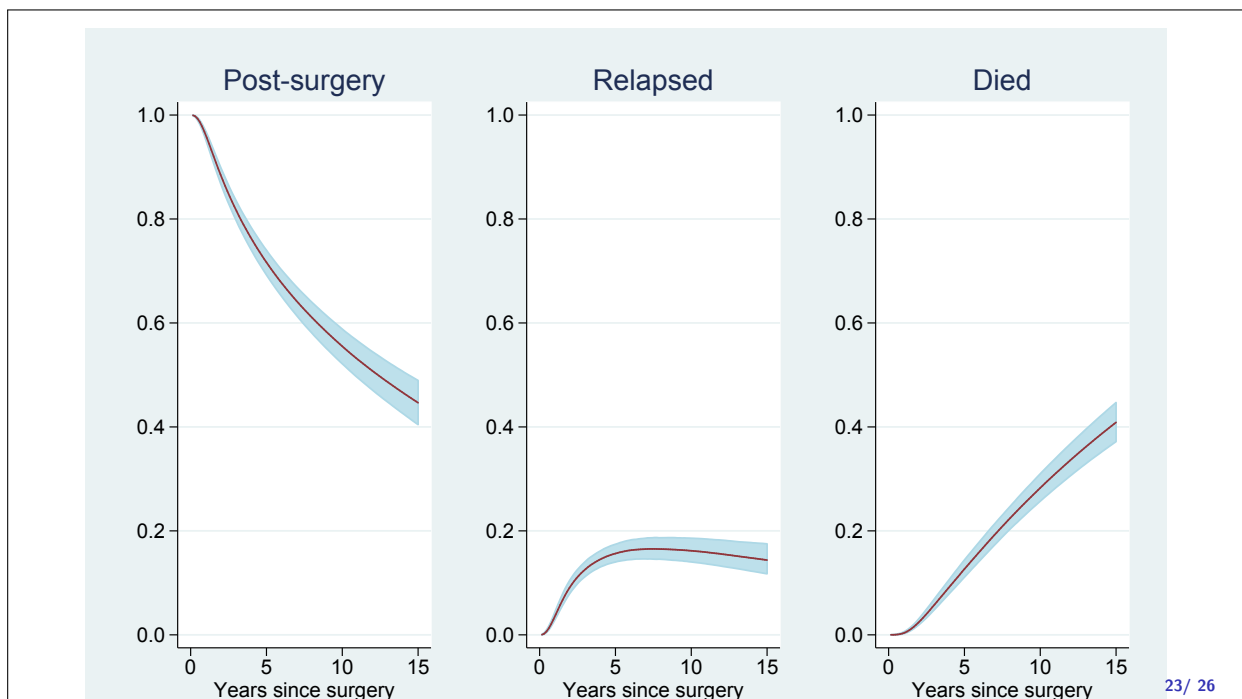
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Using the Lexis machinery

- ▶ Representation of rates fully parametrically
- ▶ Allows simple calculation of the rate function
- ▶ Simple test for proportional hazards
- ▶ State occupancy probabilities requires simulation: [simLexis](#)
 - see vignette in `Epi`
- ▶ Access to other measures such as expected residual lifetime.
- ▶ — similar machinery available in Stata:
 - ▶ `multistate`
 - ▶ `SiM` (under review): Crowther, M. J. & Lambert, P. C.: Parametric multi-state survival models: flexible modelling allowing transition-specific distributions with application to estimating clinically useful measures of effect differences. Under review.
 - ▶ Only one timescale however. . .

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History

- ▶ `Epi` package grew out of “Statistical Practice in Epidemiology with R”, annually since 2002 in Tartu Estonia
- ▶ `Lexis` machinery conceived by Martyn Plummer, IARC
- ▶ Naming originally by David Clayton & Michael Hills, `stlexis` in Stata, later renamed `stsplit`
- ▶ David Clayton wrote a `lexis` function for the `Epi` package. Obsolete now.

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EINLEITUNG
IN DIE
THEORIE
DER
BEVÖLKERUNGSSTATISTIK

VON
W. LEXIS
DR. DER STAATSWISSENSCHAFTEN UND DER PHILOSOPHIE,
O. PROFESSOR DER STATISTIK IN DORFAT.

STRASSBURG
KARL J. TRÜBNER

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Summary

- ▶ Proper representation of multistate data essential:
States, transitions, risk time
- ▶ Readable modeling code
- ▶ Calculation of state probabilities requires a simulation in any realistic situation
- ▶ **Epi** package grew out of
Statistical Practice in Epidemiology with R, **SPE**
annually since 2002 in Tartu, Estonia:
<http://bendixcarstensen.com/SPE>
- ▶ Examples of use in:
<http://bendixcarstensen.com/AdvCoh/Lexis-ex/>

Thanks for your attention

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