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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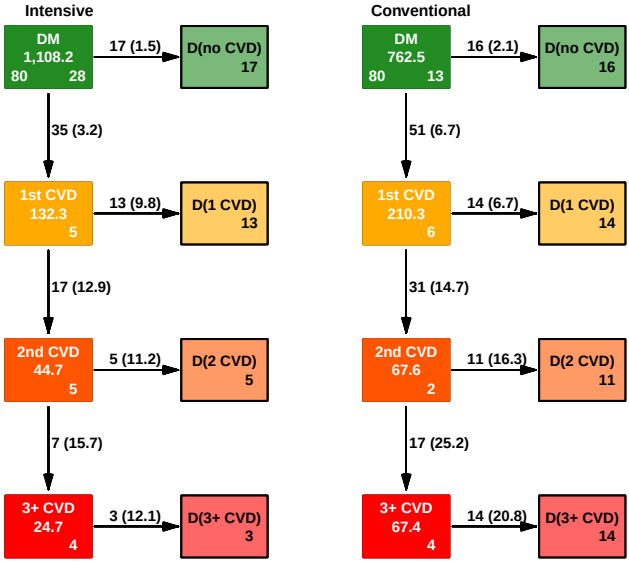
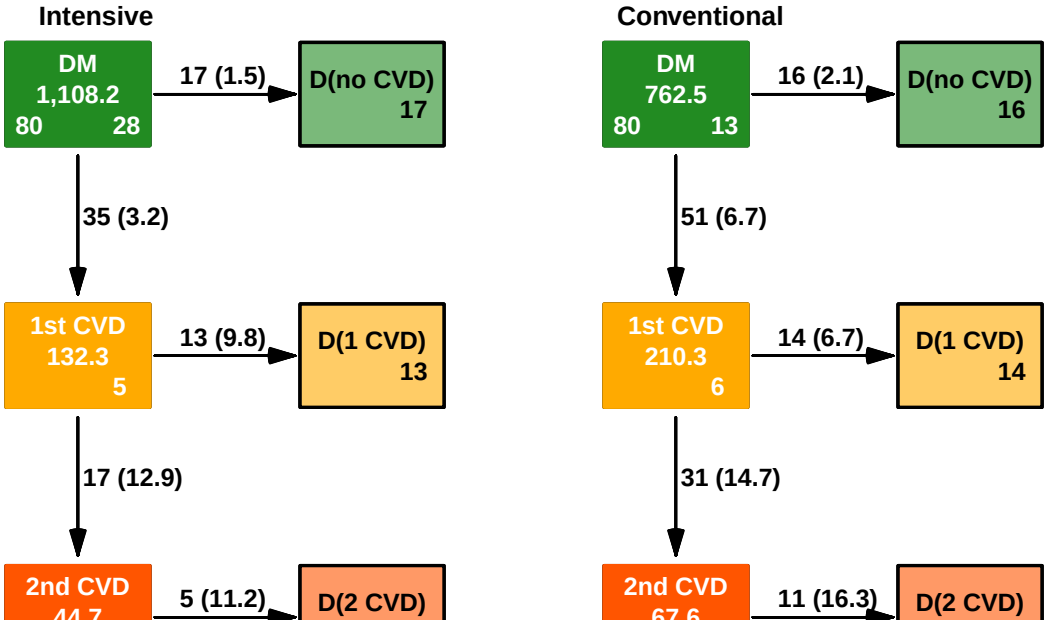
Abstract
Aims/hypothesis The aim of this work was to study the potential long-term impact of a 7.8 years intensified multifactorial pharmacological approaches. After 7.8 years the study continued as an observational follow-up with all patients receiving


Intensive
DM
1,108.2
80 28
17 (1.5)
D(no CVD)
17
35 (3.2)
1st CVD
132.3
5
13 (9.8)
D(1 CVD)
13
17 (12.9)
2nd CVD
44.7
5
5 (11.2)
D(2 CVD)
5
7 (15.7)
3+ CVD
24.7
4
3 (12.1)
D(3+ CVD)
3
Conventional
DM
762.5
80 13
16 (2.1)
D(no CVD)
16
51 (6.7)
1st CVD
210.3
6
14 (6.7)
D(1 CVD)
14
31 (14.7)
2nd CVD
67.6
2
11 (16.3)
D(2 CVD)
11
17 (25.2)
3+ CVD
67.4
4
14 (20.8)
D(3+ CVD)
14


Intensive
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1,108.2
80 28
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14
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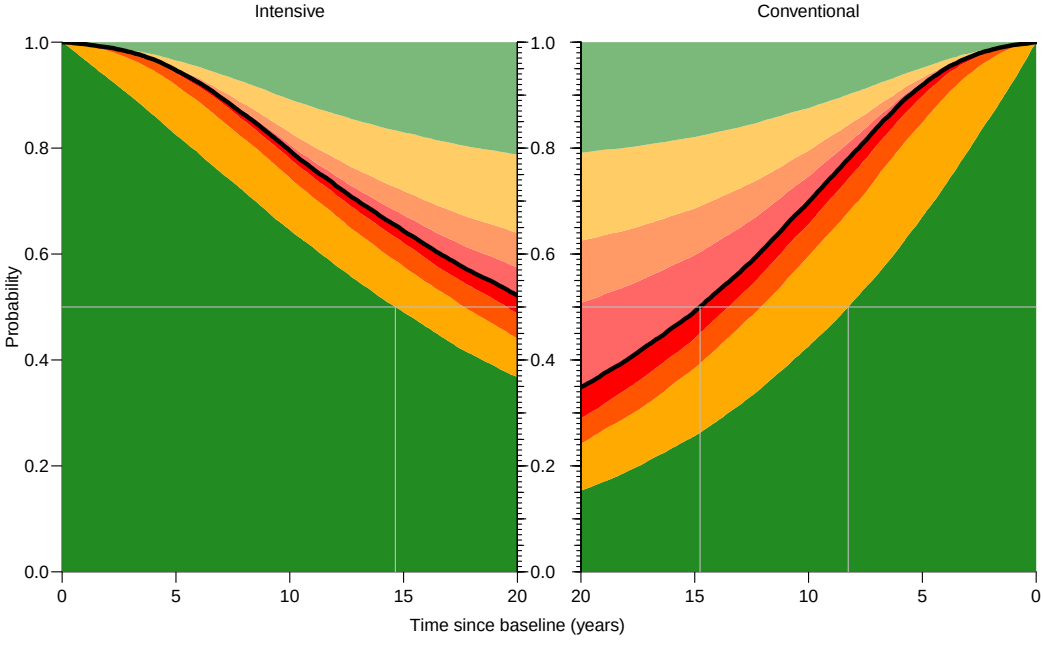
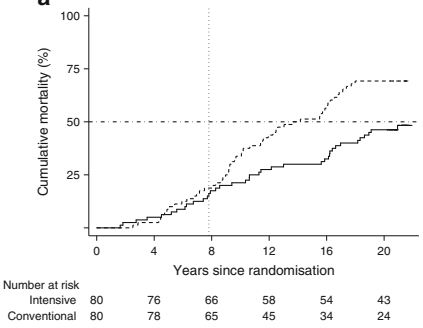
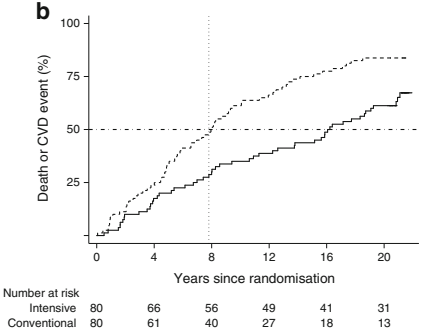
2nd CVD
67.6
11 (16.3)
D(2 CVD)

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)	


Intensive
Conventional
Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
5
10
15
20
Time since baseline (years)





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

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

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

sex		Men			Women		
state	age	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

Multistate models in practice:

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

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

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

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
```

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
```

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
```

Representation of multistate FU: Lexis

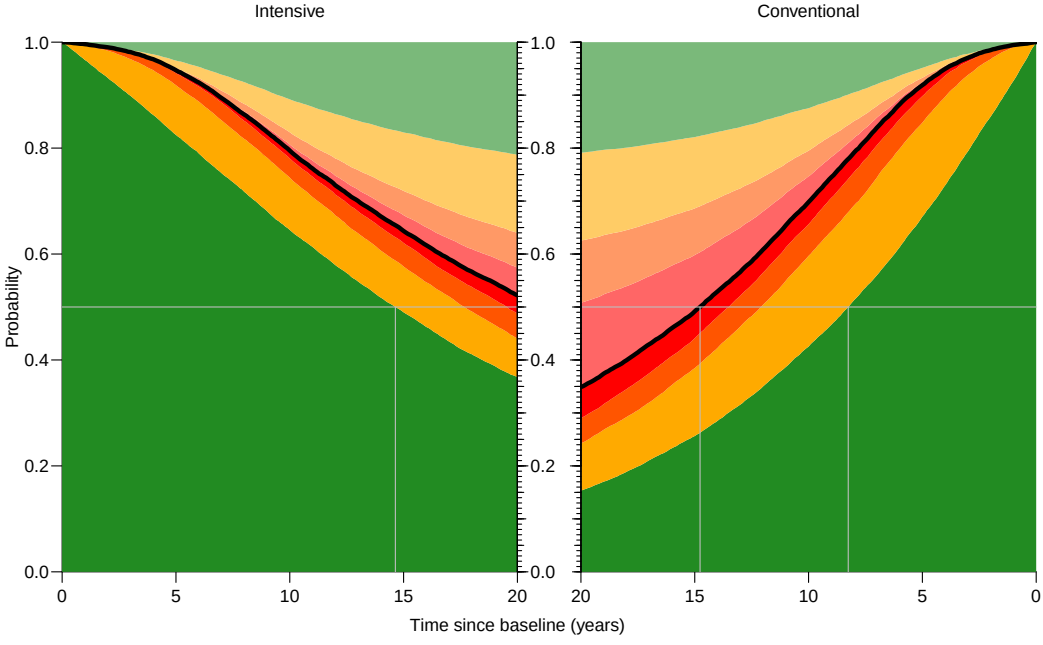
lex.id	per	age	dur	tsb	lex.dur	lex.Cst	lex.Xst	allocation	sex
5	1993.162	57.169	6.816	0.000	0.083	DM	DM	Conventional	M
5	1993.246	57.252	6.899	0.083	0.083	DM	DM	Conventional	M
...									
5	1993.829	57.836	7.483	0.667	0.083	DM	DM	Conventional	M
5	1993.912	57.919	7.566	0.750	0.047	DM	1st CVD	Conventional	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

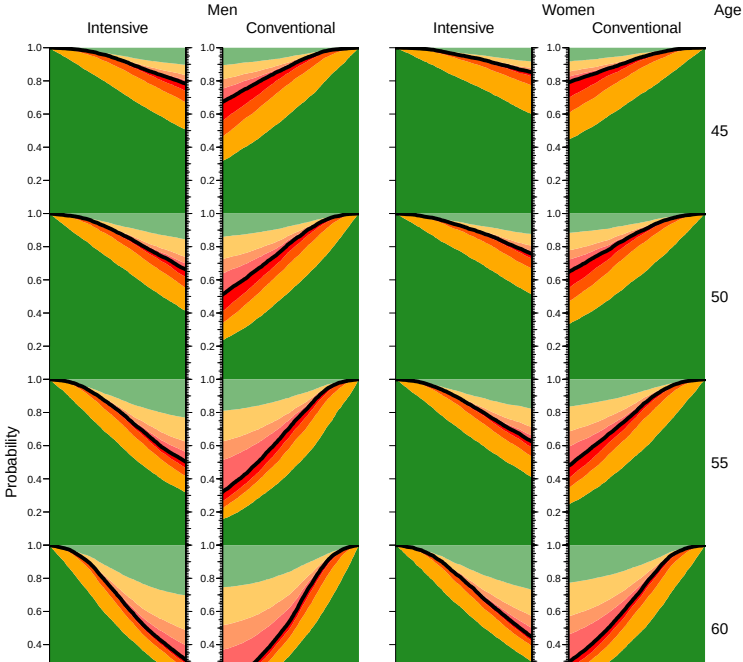
Modeling mortality rates in Lexis objects

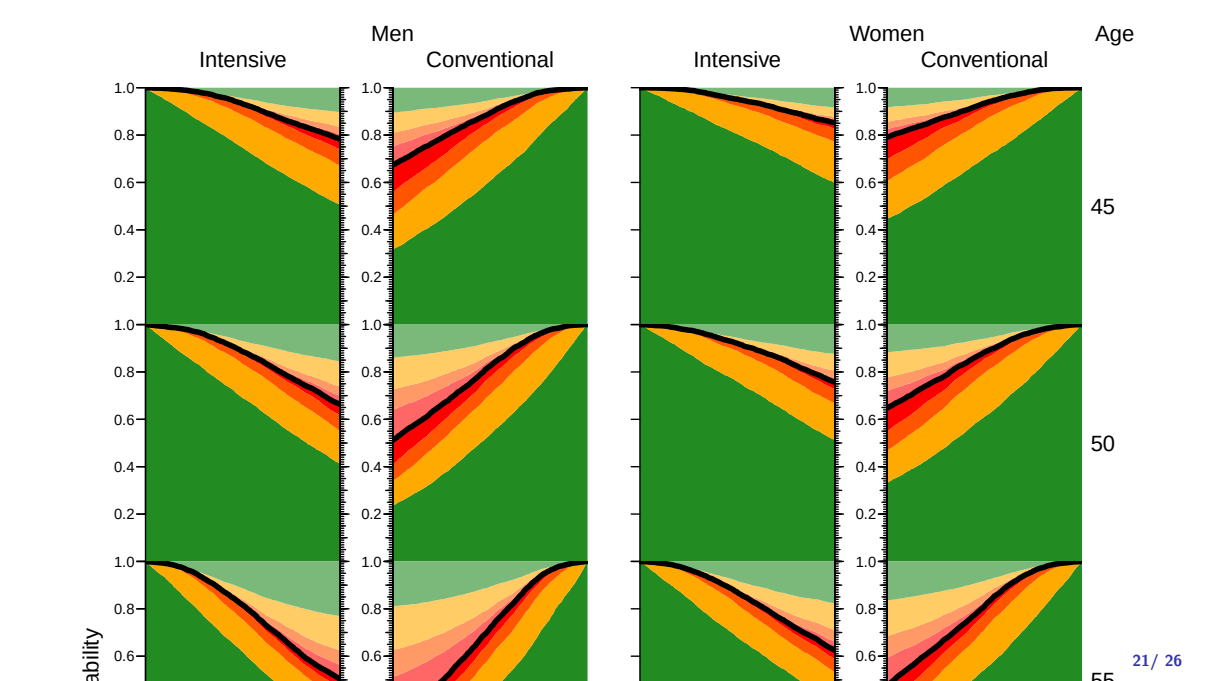
```
> dlev <- c("D(no CVD)", "D(1 CVD)",  "D(2 CVD)",  "D(3+ CVD)")
> #
> m0 <- glm( (lex.Xst %in% dlev ) ~
+            Ns( tsb, knots=d.kn ) + lex.Cst + allocation,
+            offset = log(lex.dur),
+            family = poisson,
+            data = S1 )
> #
> m1  <- update( m0, . ~ . + sex + age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

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" )
```

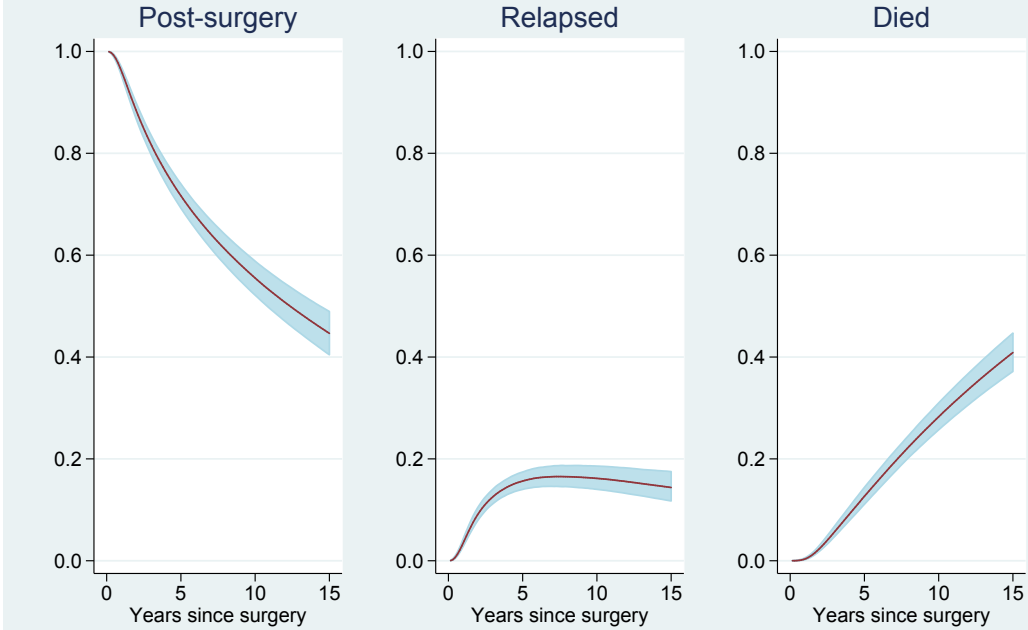

Intensive
Conventional
Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
5
10
15
20
Time since baseline (years)


Men
Women
Age
Intensive
Conventional
Intensive
Conventional
Probability
1.0
0.8
0.6
0.4
0.2
45
50
55
60


Men
Women
Age
Intensive
Conventional
Intensive
Conventional
45
50
55
1.0
0.8
0.6
0.4
0.2
ability

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 timescal however...


Post-surgery
Relapsed
Died
1.0
0.8
0.6
0.4
0.2
0.0
0
5
10
15
Years since surgery

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 Claytion wrote a `lexis` function for the `Epi` package. Obsolete now.

EINLEITUNG

IN DIE

THEORIE

DER

BEVÖLKERUNGSSTATISTIK

VON

W. LEXIS

DR. DER STAATSWISSENSCHAFTEN UND DER PHILOSOPHIE,
O. PROFESSOR DER STATISTIK IN DORPAT.

STRASSBURG

KARL J. TRÜBNER

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