

Daffodil project

Multiple heart failure events

SDC

April 2017

<http://bendixcarstensen.com>

Draft version 1

Compiled Tuesday 25th April, 2017, 15:17

from: /home/bendix/sdc/proj/daffodil/rep/multHF.tex

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Chapter 1

Recurrent heart failure

This is a documentation of the analysis of recurrent heart failures.

The data is laid out with one record per person starting index date, covering the follow-up to death, end of study or first heart failure. For patients with heart failure there are records for the time after the first, second etc. heart failure. So a person who sees 3 heart failures will have 4 records, one for the time to the first HF, one for the time between 1st and 2nd HF, one for the time between 2nd and 3rd HF and one for the time after the 3rd HF, the latter recording whether his follow-up ends by death or censoring. The 4 records have a variable indicating the number of HFs seen; it will have values 0, 1, 2 and 3, respectively. We can model the occurrence rates of (next) HF and death as depending on this.

Technically this is all encoded in the **Lexis** objects, that are updated by cutting follow-up at dates of HF; this is wrapped in the function **ncut** defined in the code. On the last page is an illustration of the follow-up for recurrent HF both in the case where drug cessation is considered a censoring and when not.

1.1 Recurrent Heart Failure

In this section we analyze the occurrence of multiple instances of heart failure after index date. Although all occurrences HF are recorded the same way, multiple occurrences indicate an increasing sickness among the patients. Thus we shall use the number of HF after index date to influence the occurrence of (the next) HF. In Denmark there are many closely spaced recordings of HF, so the data we have collected only count HF recordings at least 30 days after the previous one.

We also want to be able to control for the number of HF events *before* index date.

1.1.1 Lexis objects

We here take the matched data and set up **Lexis**-objects for the survival analyses; we first make a Lexis objects for Death as outcome:

```
> library( Epi )
> library( survival )
> print( sessionInfo(), l=F )
R version 3.3.2 (2016-10-31)
Platform: x86_64-w64-mingw32/x64 (64-bit)
```

...input from DYhf.tex

Running under: Windows Server 2012 R2 x64 (build 9600)

attached base packages:

[1] stats graphics grDevices utils datasets methods base

other attached packages:

[1] survival_2.40-1 Epi_2.7

loaded via a namespace (and not attached):

[1] cmprsk_2.2-7 MASS_7.3-45 Matrix_1.2-7.1 plyr_1.8.4
[5] parallel_3.3.2 tools_3.3.2 etm_0.6-2 Rcpp_0.12.8
[9] splines_3.3.2 grid_3.3.2 numDeriv_2016.8-1 lattice_0.20-34

> load(file = "adata.Rda")

> lls()

	name	mode	class	size
1	mset	list	data.frame	29968 195
2	oset	list	data.frame	128499 195
3	pscore	numeric	table	96 9
4	psmatch	numeric	table	95 9

> names(mset)

[1]	"pnr"	"eksd"	"epiN"	"doIx"	"doTm"
[6]	"isTm"	"prev"	"diff"	"doNPR"	"doDVDD"
[11]	"typ"	"doIns"	"doOAD"	"doDiab"	"sex"
[16]	"doBth"	"doDth"	"doDM"	"inCr"	"nnew"
[21]	"IxdR"	"Ixatc"	"doFL"	"FLdr"	"FLatc"
[26]	"doLACE"	"doLSta"	"doLBB1"	"doLARb"	"doLAlA"
[31]	"doLDHP"	"doLWtL"	"doLAsp"	"doLHCD"	"doLWrf"
[36]	"doLRPA"	"doLTHZ"	"doLDgo"	"doLAP1"	"doLCcs"
[41]	"doLDTI"	"doLDXI"	"doLAmi"	"doLFla"	"doLNHP"
[46]	"doLMetformin"	"doLGLP1"	"doLMetxSGLT2"	"doLlongIns"	"doLmixIns"
[51]	"doLDPP4"	"doLSU"	"doLintIns"	"doLfastIns"	"doLMetxDPP4"
[56]	"doLTZD"	"doLAcarbose"	"doLTZDxDPP4"	"maxH"	"frail"
[61]	"doAmp"	"doDiaEye"	"doAngina"	"doBleed"	"doCOPD"
[66]	"doPAD"	"doHF"	"doCancer"	"doDMcompl"	"doNeuro"
[71]	"doDKD"	"doHypo"	"doAtrFib"	"doMI"	"doUnstAng"
[76]	"doHmStr"	"doDiaFoot"	"doOther"	"doPeriAng"	"doIscStr"
[81]	"doTIA"	"doCKD"	"doKeto"	"doDial"	"recnum"
[86]	"C_ADIAG"	"compl"	"C_OPR"	"D_INDDTO"	"V_SENGDAGE"
[91]	"deCVDD"	"coD"	"deHF"	"deMACE"	"deMI"
[96]	"deStr"	"deAF"	"deHH"	"doHF1"	"doHF2"
[101]	"doHF3"	"doHF4"	"doHF5"	"doHF6"	"doHF7"
[106]	"doHF8"	"doHF9"	"doHF10"	"doHF11"	"doHF12"
[111]	"doHF13"	"preHF"	"postHF"	"age"	"tff"
[116]	"Ixgr"	"prv.Amp"	"prv.DiaEye"	"prv.Angina"	"prv.Bleed"
[121]	"prv.COPD"	"prv.PAD"	"prv.HF"	"prv.Cancer"	"prv.DMcompl"
[126]	"prv.Neuro"	"prv.DKD"	"prv.Hypo"	"prv.AtrFib"	"prv.MI"
[131]	"prv.UnstAng"	"prv.HmStr"	"prv.DiaFoot"	"prv.Other"	"prv.PeriAng"
[136]	"prv.IscStr"	"prv.TIA"	"prv.CKD"	"prv.Keto"	"prv.Dial"
[141]	"prv.HF1"	"prv.HF2"	"prv.HF3"	"prv.HF4"	"prv.HF5"
[146]	"prv.HF6"	"prv.HF7"	"prv.HF8"	"prv.HF9"	"prv.HF10"
[151]	"prv.HF11"	"prv.HF12"	"prv.HF13"	"pre.CVD"	"pre.Str"
[156]	"pre.FPA"	"pre.Mic"	"had.ACE"	"had.Sta"	"had.BB1"
[161]	"had.ARB"	"had.AlA"	"had.DHP"	"had.WtL"	"had.Asp"
[166]	"had.HCD"	"had.Wrf"	"had.RPA"	"had.THZ"	"had.Dgo"
[171]	"had.AP1"	"had.Ccs"	"had.DTI"	"had.DXI"	"had.Ami"
[176]	"had.Fla"	"had.NHP"	"had.Metformin"	"had.GLP1"	"had.MetxSGLT2"

```

[181] "had.longIns"    "had.mixIns"    "had.DPP4"      "had.SU"        "had.intIns"
[186] "had.fastIns"    "had.MetxDPP4"  "had.TZD"       "had.Acarbose"   "had.TZDxDPP4"
[191] "got.Ins"        "got.Hyp"       "got.CVD"       "mfac"          "psco"

```

We will follow persons from date of new use, `doIx` till death (or end of study), and we shall use the date of termination of the index treatment (`doTm`) as a time-dependent covariate.

For later use we define both the time since index (`tfi`) and current date (period — `per`) and current age (`cua`) as timescales. The latter not to be confused with age at index date, `age`.

Here is the Lexis object with follow-up till death for the matched data:

```

> mM <- Lexis( entry = list( per = doIx,
+                             cua = doIx-doBth,
+                             tfi = 0 ),
+             exit = list( per = pmin( doDth, 2016, na.rm=TRUE ) ),
+             exit.status = factor( !is.na( doDth ) & doIx < doDth & doDth<2016,
+                                   labels=c("OnDr","Dead") ),
+             data = subset( mset, is.na(doDth) | doIx < doDth ) )

```

NOTE: `entry.status` has been set to "OnDr" for all.

```

> mM <- cutLexis( mM, cut = mM$doTm,
+                 new.state = "OffDr",
+                 pre = "OnDr" )
> summary( mM )

```

Transitions:

From	To	OnDr	OffDr	Dead	Records:	Events:	Risk time:	Persons:
OnDr	OnDr	26345	2814	808	29967	3622	33289.93	29967
OnDr	OffDr	0	2722	92	2814	92	2755.62	2814
OnDr	Sum	26345	5536	900	32781	3714	36045.55	29967

```
> summary( mM, by="Ixdr" )
```

\$Met

Transitions:

From	To	OnDr	OffDr	Dead	Records:	Events:	Risk time:	Persons:
OnDr	OnDr	2640	294	42	2976	336	2636.02	2976
OnDr	OffDr	0	288	6	294	6	225.08	294
OnDr	Sum	2640	582	48	3270	342	2861.10	2976

\$SU

Transitions:

From	To	OnDr	OffDr	Dead	Records:	Events:	Risk time:	Persons:
OnDr	OnDr	2112	288	39	2439	327	2634.43	2439
OnDr	OffDr	0	281	7	288	7	273.39	288
OnDr	Sum	2112	569	46	2727	334	2907.82	2439

\$DPP

Transitions:

From	To	OnDr	OffDr	Dead	Records:	Events:	Risk time:	Persons:
OnDr	OnDr	6056	429	124	6609	553	7371.32	6609
OnDr	OffDr	0	424	5	429	5	413.94	429
OnDr	Sum	6056	853	129	7038	558	7785.26	6609

\$GLP

Transitions:

From	To	OnDr	OffDr	Dead	Records:	Events:	Risk time:	Persons:
OnDr	OnDr	2473	121	24	2618	145	3170.69	2618
OffDr	OffDr	0	116	5	121	5	132.39	121
Sum	Sum	2473	237	29	2739	150	3303.07	2618

\$SGL

Transitions:

From	To	OnDr	OffDr	Dead	Records:	Events:	Risk time:	Persons:
OnDr	OnDr	6547	849	96	7492	945	8317.48	7492
OffDr	OffDr	0	834	15	849	15	904.79	849
Sum	Sum	6547	1683	111	8341	960	9222.27	7492

\$fIns

Transitions:

From	To	OnDr	OffDr	Dead	Records:	Events:	Risk time:	Persons:
OnDr	OnDr	1376	528	201	2105	729	1930.43	2105
OffDr	OffDr	0	493	35	528	35	489.09	528
Sum	Sum	1376	1021	236	2633	764	2419.52	2105

\$iIns

Transitions:

From	To	OnDr	OffDr	Dead	Records:	Events:	Risk time:	Persons:
OnDr	OnDr	1422	127	105	1654	232	2182.07	1654
OffDr	OffDr	0	117	10	127	10	135.72	127
Sum	Sum	1422	244	115	1781	242	2317.79	1654

\$mIns

Transitions:

From	To	OnDr	OffDr	Dead	Records:	Events:	Risk time:	Persons:
OnDr	OnDr	682	71	43	796	114	1135.36	796
OffDr	OffDr	0	66	5	71	5	80.28	71
Sum	Sum	682	137	48	867	119	1215.63	796

\$lIns

Transitions:

From	To	OnDr	OffDr	Dead	Records:	Events:	Risk time:	Persons:
OnDr	OnDr	3037	107	134	3278	241	3912.13	3278
OffDr	OffDr	0	103	4	107	4	100.94	107
Sum	Sum	3037	210	138	3385	245	4013.07	3278

1.1.2 Recurrent HF

Once we have persons followed till death we can split the follow-up further by the dates of HF post index. In order to be able to separate follow-up pre and post drug-cessation we cut two subsets of the Lexis objects separately, but the code is the same, so we stash it in a function:

```
> ncut <-
+ function( Lx, abs="Dead" )
+ {
+   for( i in 1:13 )
+   {
+     # where is the date of the i'th HF event
+     wh <- match( paste("doHF",i,sep=""), names(Lx) )
+     # cut at that
+     Lx <- cutLexis( Lx, cut = Lx[,wh] ,
+                     new.state = paste(i,"HF") ,
+                     precursor = setdiff(levels(Lx),abs) )
+     cat( i, " " )
+   }
+   Lx
+ }
> mMon <- ncut( subset( mM, lex.Cst=="OnDr" ), abs=c("OffDr","Dead") )
> mMoff <- ncut( subset( mM, lex.Cst=="OffDr" ) )
> system.time( mMall <- ncut( mM ) )
> save( mMon, mMoff, mMall, file="../data/recHF.Rda" )
```

With this in place we can show the total number of HF events and total number of PY:

```
> load( file="../data/recHF.Rda" )
> round( addmargins( onDrFU <-
+ xtabs( cbind( nHF = lex.Xst %in% levels(lex.Xst)[2:14] & lex.Xst!=lex.Cst,
+               PY = lex.dur ) ~ Ixgr,
+         data = mMon ), 1 ) )
Ixgr      nHF      PY
Comp      403 24972
SGLT2      85  8317
Sum        488 33290

> round( addmargins( allFU <-
+ xtabs( cbind( nHF = lex.Xst %in% levels(lex.Xst)[3:15] & lex.Xst!=lex.Cst,
+               PY = lex.dur ) ~ Ixgr,
+         data = mMall ), 1 ) )
Ixgr      nHF      PY
Comp      462 26823
SGLT2     100  9222
Sum        562 36046
```

A slightly more detailed picture is obtained by looking at all transitions between the defined states:

```
> summary( mMon )
Transitions:
  To
From  OnDr 1 HF 2 HF 3 HF 4 HF 5 HF 6 HF 7 HF 8 HF 9 HF 10 HF 11 HF 12 HF 13 HF OffDr
OnDr 26044 369   0   0   0   0   0   0   0   0   0   0   0   0   0   0   0   0   2791
1 HF   0  226  90   0   0   0   0   0   0   0   0   0   0   0   0   0   0   16
2 HF   0   0  59  18   0   0   0   0   0   0   0   0   0   0   0   0   0   6
```

3 HF	0	0	0	10	7	0	0	0	0	0	0	0	0	0	1
4 HF	0	0	0	0	4	2	0	0	0	0	0	0	0	0	0
5 HF	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0
6 HF	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0
Sum	26044	595	149	28	11	2	4	0	0	0	0	0	0	0	2814

Transitions:

To

From	Dead	Records:	Events:	Risk time:	Persons:
OnDr	763	29967	3923	33012.72	29967
1 HF	37	369	143	216.90	369
2 HF	7	90	31	47.96	90
3 HF	0	18	8	8.19	18
4 HF	1	7	3	2.83	7
5 HF	0	2	2	0.88	2
6 HF	0	2	0	0.46	2
Sum	808	30455	4110	33289.93	29967

`> summary( mMoff )`

Transitions:

To

From	OnDr	OffDr	1 HF	2 HF	3 HF	4 HF	5 HF	6 HF	7 HF	8 HF	9 HF	10 HF	11 HF	12 HF	13 HF
OffDr	0	2671	40	0	0	0	0	0	0	0	0	0	0	0	0
1 HF	0	0	33	16	0	0	0	0	0	0	0	0	0	0	0
2 HF	0	0	0	12	5	0	0	0	0	0	0	0	0	0	0
3 HF	0	0	0	0	3	3	0	0	0	0	0	0	0	0	0
4 HF	0	0	0	0	0	1	2	0	0	0	0	0	0	0	0
5 HF	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0
6 HF	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
7 HF	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
8 HF	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0
9 HF	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
10 HF	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
11 HF	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
12 HF	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
13 HF	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Sum	0	2671	73	28	8	4	3	1	1	1	1	1	1	1	2

Transitions:

To

From	Dead	Records:	Events:	Risk time:	Persons:
OffDr	80	2791	120	2707.10	2791
1 HF	7	56	23	38.39	56
2 HF	5	22	10	6.08	22
3 HF	0	6	3	1.04	6
4 HF	0	3	2	1.13	3
5 HF	0	2	1	0.38	2
6 HF	0	1	1	0.34	1
7 HF	0	1	1	0.17	1
8 HF	0	1	1	0.25	1
9 HF	0	1	1	0.31	1
10 HF	0	1	1	0.10	1
11 HF	0	1	1	0.10	1
12 HF	0	1	1	0.17	1
13 HF	0	1	0	0.06	1
Sum	92	2888	166	2755.62	2814

`> summary( mMall )`

Transitions:

To

From	OnDr	OffDr	1 HF	2 HF	3 HF	4 HF	5 HF	6 HF	7 HF	8 HF	9 HF	10 HF	11 HF	12 HF	13 HF
OnDr	26044	2791	369	0	0	0	0	0	0	0	0	0	0	0	0
OffDr	0	2671	40	0	0	0	0	0	0	0	0	0	0	0	0
1 HF	0	0	275	106	0	0	0	0	0	0	0	0	0	0	0
2 HF	0	0	0	77	23	0	0	0	0	0	0	0	0	0	0
3 HF	0	0	0	0	14	10	0	0	0	0	0	0	0	0	0
4 HF	0	0	0	0	0	5	4	0	0	0	0	0	0	0	0
5 HF	0	0	0	0	0	0	1	3	0	0	0	0	0	0	0
6 HF	0	0	0	0	0	0	0	2	1	0	0	0	0	0	0
7 HF	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
8 HF	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0
9 HF	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
10 HF	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
11 HF	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
12 HF	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
13 HF	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Sum	26044	5462	684	183	37	15	5	5	1	1	1	1	1	1	2

Transitions:

From	To	Dead	Records:	Events:	Risk time:	Persons:
OnDr	OnDr	763	29967	3923	33012.72	29967
OffDr	OffDr	80	2791	120	2707.10	2791
1 HF	1 HF	44	425	150	255.29	409
2 HF	2 HF	12	112	35	54.04	106
3 HF	3 HF	0	24	10	9.23	23
4 HF	4 HF	1	10	5	3.97	10
5 HF	5 HF	0	4	3	1.26	4
6 HF	6 HF	0	3	1	0.80	3
7 HF	7 HF	0	1	1	0.17	1
8 HF	8 HF	0	1	1	0.25	1
9 HF	9 HF	0	1	1	0.31	1
10 HF	10 HF	0	1	1	0.10	1
11 HF	11 HF	0	1	1	0.10	1
12 HF	12 HF	0	1	1	0.17	1
13 HF	13 HF	0	1	0	0.06	1
Sum	Sum	900	33343	4253	36045.55	29967

From these summaries we see that nothing beyond 5 HF instances is of relevance, so we pool 5–13 to 5+:

```

> levels( mMon )
[1] "OnDr" "1 HF" "2 HF" "3 HF" "4 HF" "5 HF" "6 HF" "7 HF" "8 HF" "9 HF"
[11] "10 HF" "11 HF" "12 HF" "13 HF" "OffDr" "Dead"

> levels( mMoff )
[1] "OnDr" "OffDr" "1 HF" "2 HF" "3 HF" "4 HF" "5 HF" "6 HF" "7 HF" "8 HF"
[11] "9 HF" "10 HF" "11 HF" "12 HF" "13 HF" "Dead"

> levels( mMall )
[1] "OnDr" "OffDr" "1 HF" "2 HF" "3 HF" "4 HF" "5 HF" "6 HF" "7 HF" "8 HF"
[11] "9 HF" "10 HF" "11 HF" "12 HF" "13 HF" "Dead"

> mMon <- Relevel( mMon , list(1,15,2,3,4,5,"5+ HF"=6:14,16), print=F, first=F )
> mMoff <- Relevel( mMoff, list("noHF"=1:2,3,4,5,6,"5+ HF"=7:15,16), print=F )
> mMall <- Relevel( mMall, list("noHF"=1:2,3,4,5,6,"5+ HF"=7:15,16), print=F )
> summary( mMon )

```

Transitions:

From	To	OnDr	OffDr	1 HF	2 HF	3 HF	4 HF	5+ HF	Dead	Records:	Events:	Risk time:
OnDr		26044	2791	369	0	0	0	0	763	29967	3923	33012.72
1 HF		0	16	226	90	0	0	0	37	369	143	216.90
2 HF		0	6	0	59	18	0	0	7	90	31	47.96
3 HF		0	1	0	0	10	7	0	0	18	8	8.19
4 HF		0	0	0	0	0	4	2	1	7	3	2.83
5+ HF		0	0	0	0	0	0	4	0	4	0	1.33
Sum		26044	2814	595	149	28	11	6	808	30455	4108	33289.93

Transitions:

From	To	Persons:
OnDr		29967
1 HF		369
2 HF		90
3 HF		18
4 HF		7
5+ HF		2
Sum		29967

> summary(mMoff)

Transitions:

From	To	noHF	1 HF	2 HF	3 HF	4 HF	5+ HF	Dead	Records:	Events:	Risk time:	Persons:
noHF		2671	40	0	0	0	0	80	2791	120	2707.10	2791
1 HF		0	33	16	0	0	0	7	56	23	38.39	56
2 HF		0	0	12	5	0	0	5	22	10	6.08	22
3 HF		0	0	0	3	3	0	0	6	3	1.04	6
4 HF		0	0	0	0	1	2	0	3	2	1.13	3
5+ HF		0	0	0	0	0	10	0	10	0	1.88	2
Sum		2671	73	28	8	4	12	92	2888	158	2755.62	2814

> summary(mMall)

Transitions:

From	To	noHF	1 HF	2 HF	3 HF	4 HF	5+ HF	Dead	Records:	Events:	Risk time:	Persons:
noHF		31506	409	0	0	0	0	843	32758	1252	35719.81	29967
1 HF		0	275	106	0	0	0	44	425	150	255.29	409
2 HF		0	0	77	23	0	0	12	112	35	54.04	106
3 HF		0	0	0	14	10	0	0	24	10	9.23	23
4 HF		0	0	0	0	5	4	1	10	5	3.97	10
5+ HF		0	0	0	0	0	14	0	14	0	3.21	4
Sum		31506	684	183	37	15	18	900	33343	1452	36045.55	29967

```
> par( mfrow=c(2,1) )
> wh <- list( x=c( 5,60,15,31,69,85,95,50),
+            y=c(10,50,50,90,90,50,10,10) )
> boxes.Lexis( mMon , boxpos=wh, scale.R=100, hmult=1.5, wmult=1.5, #show.BE=TRUE,
+             col.arr=c("black",gray(c(5,7)/10))[c(3,1,2,3,1,2,3,1,2,3,1,1,2)],
+             pos.arr=c(0.45,0.35)[c(2,1,1,2,1,2,1,1,1,1,1,1,1)],
+             col.txt=c("black",gray(c(5,7)/10))[c(1,3,1,1,1,1,1,2)] )
> text( 0, 95, "On drug", adj=c(0,1), cex=2 )
> xm2 <- function(x) x[-2]
> # boxes( mMoff, boxpos=lapply(wh,xm2), scale.R=100 )
> # text( 5, 95, "Off drug", adj=c(0,1), cex=2 )
> boxes( mMall, boxpos=lapply(wh,xm2), scale.R=100, hmult=1.5, wmult=1.5, #show.BE=TRUE,
```

```

+      col.arr=c("black",gray(0.5))[c(1,2,1,2,1,2,1,1,2)],
+      col.txt=c("black",gray(0.5))[c(1,1,1,1,1,1,2)] )
> text( 0, 95, "All FU", adj=c(0,1), cex=2 )

```

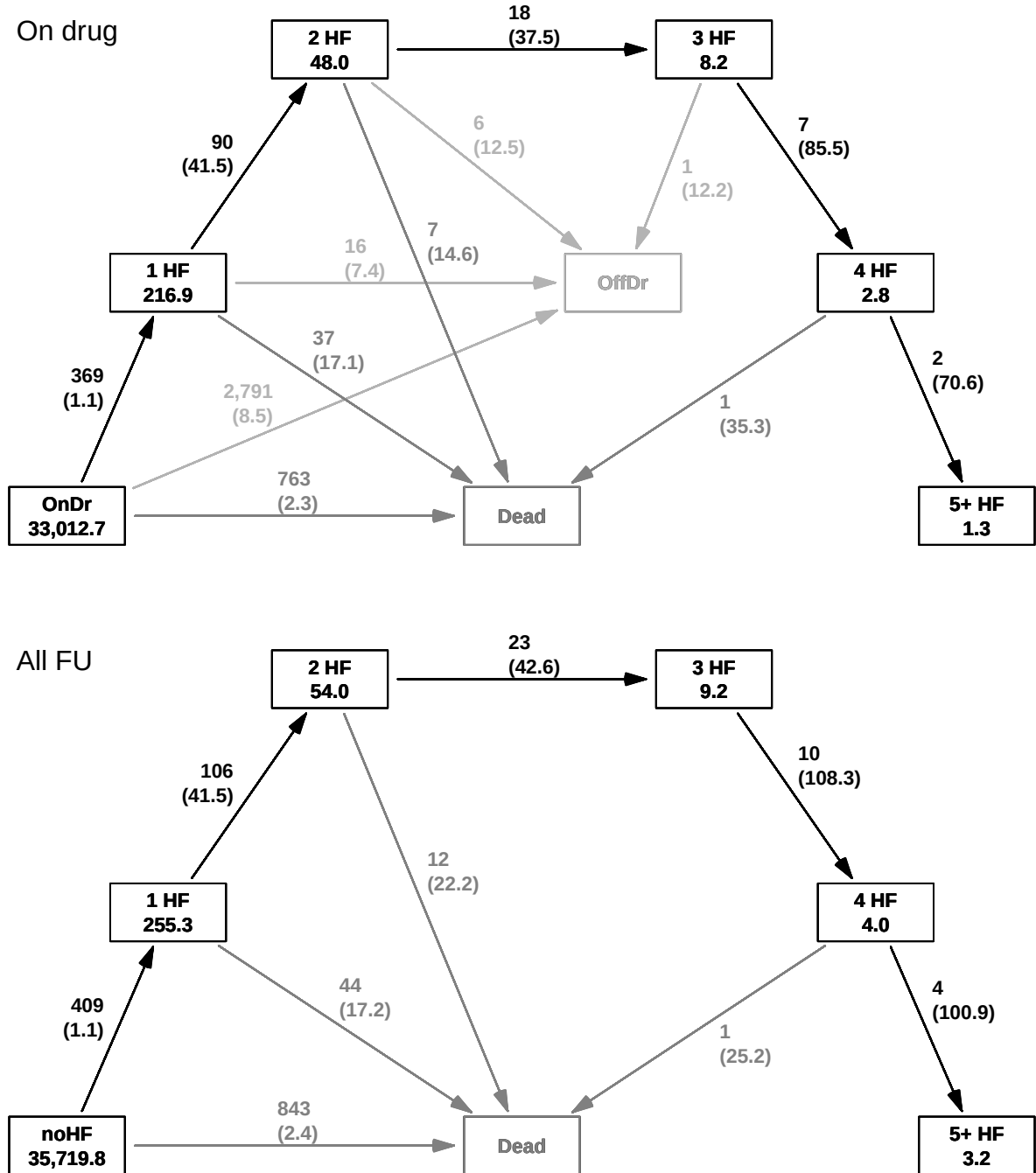


Figure 1.1: Transitions between states of HF after index. Previous occurrence of HF is ignored in this analysis. The numbers in the boxes are the number of person-years, the numbers on (the l.h.s. of) the arrows are the number of transitions and rates per 100 PY.

1.1.3 Analysis of recurrent HF

The following analyses are simple Poisson-analyses assuming constant rates across the follow-up, and quantifying the effect of SGLT2.

The “0” models are those that assume that occurrence of HF does not influence the occurrence of subsequent HF, while the “1” models allow the number of occurrences to influence rates of the next occurrence. Models “2” assumes that it is only ever HF (that is the first) that is of importance and models “3” investigates whether there is a differential effect of SGLT2 prescription between persons with and without HF.

```
> levels( mMon )
[1] "OnDr" "OffDr" "1 HF" "2 HF" "3 HF" "4 HF" "5+ HF" "Dead"
> ( hf14 <- levels( mMon )[3:6] )
[1] "1 HF" "2 HF" "3 HF" "4 HF"

> m0 <- glm( ( lex.Xst %in% levels(mMon)[3:7] & lex.Xst!=lex.Cst ) ~ Ixgr,
+           offset = log( lex.dur ),
+           family = poisson,
+           data = subset(mMon,lex.Cst!="5+") )
> m1 <- update( m0, . ~ . + factor( lex.Cst ) )
> m2 <- update( m0, . ~ . + I( lex.Cst %in% levels(mMon)[3:6] ) )
> m3 <- update( m0, . ~ - Ixgr + I( lex.Cst %in% levels(mMon)[3:6] ) +
+           I( lex.Cst %in% levels(mMon)[3:6] ):Ixgr )
> round( ci.exp( m0 ), 3 )

              exp(Est.)  2.5% 97.5%
(Intercept)      0.016 0.015 0.018
IxgrSGLT2         0.636 0.504 0.804

> round( ci.exp( m1 ), 3 )

              exp(Est.)  2.5%          97.5%
(Intercept)      0.012 0.011 1.400000e-02
IxgrSGLT2         0.679 0.537 8.590000e-01
factor(lex.Cst)1 HF 36.654 29.108 4.615700e+01
factor(lex.Cst)2 HF 32.464 20.221 5.212100e+01
factor(lex.Cst)3 HF 74.246 35.143 1.568580e+02
factor(lex.Cst)4 HF 58.131 14.474 2.334640e+02
factor(lex.Cst)5+ HF  0.001 0.000 1.588254e+175

> round( ci.exp( m2 ), 3 )

              exp(Est.)  2.5% 97.5%
(Intercept)      0.012 0.011 0.014
IxgrSGLT2         0.678 0.536 0.857
I(lex.Cst %in% levels(mMon)[3:6])TRUE 37.278 30.272 45.904

> round( ci.exp( m3 ), 3 )

              exp(Est.)  2.5% 97.5%
(Intercept)      0.012 0.011 0.014
I(lex.Cst %in% levels(mMon)[3:6])TRUE 37.721 30.107 47.261
I(lex.Cst %in% levels(mMon)[3:6])FALSE:IxgrSGLT2 0.689 0.530 0.895
I(lex.Cst %in% levels(mMon)[3:6])TRUE:IxgrSGLT2 0.637 0.376 1.079

> cm0 <- update( m0, . ~ . + I(doIx-doBth) + sex + I(doIx-doDM)
+           + prv.MI + prv.HF + prv.AtrFib + frail
+           + had.BB1 + had.NHP + had.ALA + had.ACE )
> cm1 <- update( cm0, . ~ . + factor( lex.Cst ) )
> anova( cm1, cm0, m0, m1, m2, m3, test="Chisq" )
```

Analysis of Deviance Table

```

Model 1: (lex.Xst %in% levels(mMon)[3:7] & lex.Xst != lex.Cst) ~ Ixgr +
  I(doIx - doBth) + sex + I(doIx - doDM) + prv.MI + prv.HF +
  prv.AtrFib + frail + had.BBl + had.NHP + had.A1A + had.ACE +
  factor(lex.Cst)
Model 2: (lex.Xst %in% levels(mMon)[3:7] & lex.Xst != lex.Cst) ~ Ixgr +
  I(doIx - doBth) + sex + I(doIx - doDM) + prv.MI + prv.HF +
  prv.AtrFib + frail + had.BBl + had.NHP + had.A1A + had.ACE
Model 3: (lex.Xst %in% levels(mMon)[3:7] & lex.Xst != lex.Cst) ~ Ixgr
Model 4: (lex.Xst %in% levels(mMon)[3:7] & lex.Xst != lex.Cst) ~ Ixgr +
  factor(lex.Cst)
Model 5: (lex.Xst %in% levels(mMon)[3:7] & lex.Xst != lex.Cst) ~ Ixgr +
  I(lex.Cst %in% levels(mMon)[3:6])
Model 6: (lex.Xst %in% levels(mMon)[3:7] & lex.Xst != lex.Cst) ~ I(lex.Cst %in%
  levels(mMon)[3:6]) + I(lex.Cst %in% levels(mMon)[3:6]):Ixgr
  Resid. Df Resid. Dev  Df Deviance Pr(>Chi)

```

```

1      30437      3845.9
2      30442      4004.3  -5   -158.32  <2e-16 ***
3      30453      5161.5 -11  -1157.20  <2e-16 ***
4      30448      4571.1   5    590.39  <2e-16 ***
5      30452      4574.5  -4    -3.44   0.4877
6      30451      4574.5   1     0.07   0.7914
---

```

```

Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

```

> levels( mMall )

```

```

[1] "noHF" "1 HF" "2 HF" "3 HF" "4 HF" "5+ HF" "Dead"

```

```

> t0 <- glm( ( lex.Xst %in% levels(mMall)[2:6] & lex.Xst!=lex.Cst ) ~ Ixgr,
+           offset = log( lex.dur ),
+           family = poisson,
+           data = subset(mMall,lex.Cst!="5+") )
> t1 <- update( t0, . ~ . + factor( lex.Cst ) )
> t2 <- update( t0, . ~ . + I( lex.Cst %in% levels(mMall)[2:5] ) )
> t3 <- update( t0, . ~ - Ixgr + I( lex.Cst %in% levels(mMall)[2:5] ) +
+           I( lex.Cst %in% levels(mMall)[2:5] ):Ixgr )
> round( ci.exp( t0 ), 3 )

```

```

              exp(Est.)  2.5% 97.5%
(Intercept)      0.017 0.015 0.018
IxgrSGLT2         0.643 0.518 0.799

```

```

> round( ci.exp( t1 ), 3 )

```

```

              exp(Est.)  2.5% 97.5%
(Intercept)      0.012 0.011 1.400000e-02
IxgrSGLT2         0.690 0.555 8.570000e-01
factor(lex.Cst)1 HF  35.849 28.951 4.439000e+01
factor(lex.Cst)2 HF  36.218 23.791 5.513500e+01
factor(lex.Cst)3 HF  91.209 48.693 1.708450e+02
factor(lex.Cst)4 HF  81.078 30.258 2.172520e+02
factor(lex.Cst)5+ HF   0.000 0.000 2.908195e+156

```

```

> round( ci.exp( t2 ), 3 )

```

```

              exp(Est.)  2.5% 97.5%
(Intercept)      0.012 0.011 0.014
IxgrSGLT2         0.684 0.551 0.850
I(lex.Cst %in% levels(mMall)[2:5])TRUE  38.117 31.503 46.120

```

```

> round( ci.exp( t3 ), 3 )

```

```

                                exp(Est.)  2.5%  97.5%
(Intercept)                    0.012  0.011  0.014
I(lex.Cst %in% levels(mMall)[2:5])TRUE      38.974 31.682 47.944
I(lex.Cst %in% levels(mMall)[2:5])FALSE:IxgrSGLT2  0.706  0.553  0.901
I(lex.Cst %in% levels(mMall)[2:5])TRUE:IxgrSGLT2  0.612  0.382  0.982
> ct0 <- update( t0, . ~ . + I(doIx-doBth) + sex + I(doIx-doDM)
+                               + prv.MI + prv.HF + prv.AtrFib + frail
+                               + had.BB1 + had.NHP + had.A1A + had.ACE )
> ct1 <- update( ct0, . ~ . + factor( lex.Cst ) )
> anova( ct1, ct0, t0, t1, t2, t3, test="Chisq" )

Analysis of Deviance Table

Model 1: (lex.Xst %in% levels(mMall)[2:6] & lex.Xst != lex.Cst) ~ Ixgr +
  I(doIx - doBth) + sex + I(doIx - doDM) + prv.MI + prv.HF +
  prv.AtrFib + frail + had.BB1 + had.NHP + had.A1A + had.ACE +
  factor(lex.Cst)
Model 2: (lex.Xst %in% levels(mMall)[2:6] & lex.Xst != lex.Cst) ~ Ixgr +
  I(doIx - doBth) + sex + I(doIx - doDM) + prv.MI + prv.HF +
  prv.AtrFib + frail + had.BB1 + had.NHP + had.A1A + had.ACE
Model 3: (lex.Xst %in% levels(mMall)[2:6] & lex.Xst != lex.Cst) ~ Ixgr
Model 4: (lex.Xst %in% levels(mMall)[2:6] & lex.Xst != lex.Cst) ~ Ixgr +
  factor(lex.Cst)
Model 5: (lex.Xst %in% levels(mMall)[2:6] & lex.Xst != lex.Cst) ~ Ixgr +
  I(lex.Cst %in% levels(mMall)[2:5])
Model 6: (lex.Xst %in% levels(mMall)[2:6] & lex.Xst != lex.Cst) ~ I(lex.Cst %in%
  levels(mMall)[2:5]) + I(lex.Cst %in% levels(mMall)[2:5]):Ixgr
  Resid. Df Resid. Dev  Df Deviance Pr(>Chi)
1      33325      4325.2
2      33330      4527.7  -5   -202.53  < 2e-16 ***
3      33341      5820.2 -11  -1292.47  < 2e-16 ***
4      33336      5092.1   5    728.13  < 2e-16 ***
5      33340      5100.2  -4    -8.15  0.08622 .
6      33339      5099.9   1     0.28  0.59783
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

> round( rbind( ci.exp( t0, subset="Ixgr", pval=TRUE ),
+               ci.exp( t1, subset="Ixgr", pval=TRUE ),
+               ci.exp( ct0, subset="Ixgr", pval=TRUE ),
+               ci.exp( ct1, subset="Ixgr", pval=TRUE ) ), 3 )
                                exp(Est.)  2.5%  97.5%      P
IxgrSGLT2      0.643  0.518  0.799  0.000
IxgrSGLT2      0.690  0.555  0.857  0.001
IxgrSGLT2      0.670  0.539  0.833  0.000
IxgrSGLT2      0.708  0.569  0.881  0.002

```

From the model summaries it is seen that the naive model assuming that HF rates is identical between persons with no HF and persons with one or more gives a downward biased estimate, due to confounding. It is also seen from comparing model 1 and 2 that there is not compelling evidence of increasing HF rates once the first HF has occurred. Presumably due to lack of data — remember the figures. Finally, the comparison of model 2 and 3 clearly shows that there is no interaction between SGLT2 and number of HF, so the conclusion here is that models 1 or 2 provide the estimate of that are most likely to be unconfounded. The change in effect estimate (on log-scale) from model 0 to 1 is in the order of magnitude of 1 s.e. of the estimate, whereas the difference between the estimates from models 1 and 2 is in the order of magnitude of 1% of the s.e.

1.1.4 Including death as outcome

If we also want to include death as outcome, that is count the transitions to death along with the HF transitions, we just use the same code, but update the definitions of the types of events counted. Note that we now also include the state “5+HF” in the risk set, because the persons there are at risk of dying.

```
> levels( mMon )
[1] "OnDr" "OffDr" "1 HF" "2 HF" "3 HF" "4 HF" "5+ HF" "Dead"
> M0 <- glm( ( lex.Xst %in% levels(mMon)[3:8] & lex.Xst!=lex.Cst ) ~ Ixgr,
+           offset = log( lex.dur ),
+           family = poisson,
+           data = mMon )
> M1 <- update( M0, . ~ . + factor( lex.Cst ) )
> M2 <- update( M0, . ~ . + I( lex.Cst %in% levels(mMon)[3:7] ) )
> M3 <- update( M0, . ~ . - Ixgr + I( lex.Cst %in% levels(mMon)[3:7] ) +
+           I( lex.Cst %in% levels(mMon)[3:7] ):Ixgr )
> round( ci.exp( M0 ), 3 )

              exp(Est.)  2.5% 97.5%
(Intercept)      0.045 0.042 0.047
IxgrSGLT2         0.488 0.417 0.571

> round( ci.exp( M1 ), 3 )

              exp(Est.)  2.5%          97.5%
(Intercept)          0.039 0.037 4.200000e-02
IxgrSGLT2             0.504 0.431 5.900000e-01
factor(lex.Cst)1 HF   16.728 13.925 2.009700e+01
factor(lex.Cst)2 HF   14.400  9.688 2.140600e+01
factor(lex.Cst)3 HF   23.770 11.305 4.997600e+01
factor(lex.Cst)4 HF   27.068  8.715 8.407000e+01
factor(lex.Cst)5+ HF    0.000  0.000 7.899689e+104

> round( ci.exp( M2 ), 3 )

              exp(Est.)  2.5% 97.5%
(Intercept)          0.039 0.037 0.042
IxgrSGLT2             0.504 0.431 0.590
I(lex.Cst %in% levels(mMon)[3:7])TRUE  16.555 14.041 19.520

> round( ci.exp( M3 ), 3 )

              exp(Est.)  2.5% 97.5%
(Intercept)          0.039 0.037 0.042
I(lex.Cst %in% levels(mMon)[3:7])TRUE  16.286 13.657 19.422
I(lex.Cst %in% levels(mMon)[3:7])FALSE:IxgrSGLT2  0.497 0.420 0.587
I(lex.Cst %in% levels(mMon)[3:7])TRUE:IxgrSGLT2   0.569 0.357 0.909

> anova( M0, M1, M2, M3, test="Chisq" )

Analysis of Deviance Table

Model 1: (lex.Xst %in% levels(mMon)[3:8] & lex.Xst != lex.Cst) ~ Ixgr
Model 2: (lex.Xst %in% levels(mMon)[3:8] & lex.Xst != lex.Cst) ~ Ixgr +
  factor(lex.Cst)
Model 3: (lex.Xst %in% levels(mMon)[3:8] & lex.Xst != lex.Cst) ~ Ixgr +
  I(lex.Cst %in% levels(mMon)[3:7])
Model 4: (lex.Xst %in% levels(mMon)[3:8] & lex.Xst != lex.Cst) ~ I(lex.Cst %in%
  levels(mMon)[3:7]) + I(lex.Cst %in% levels(mMon)[3:7]):Ixgr
Resid. Df Resid. Dev Df Deviance Pr(>Chi)
1      30453      11010
2      30448      10422  5    589.02 <2e-16 ***
```

```

3      30452      10425 -4      -3.69  0.4502
4      30451      10425  1       0.28  0.5945
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

> levels( mMall )
[1] "noHF" "1 HF" "2 HF" "3 HF" "4 HF" "5+ HF" "Dead"

> T0 <- glm( ( lex.Xst %in% levels(mMall)[2:7] & lex.Xst!=lex.Cst ) ~ Ixgr,
+           offset = log( lex.dur ),
+           family = poisson,
+           data = mMall )
> T1 <- update( T0, . ~ . + factor( lex.Cst ) )
> T2 <- update( T0, . ~ . + I( lex.Cst %in% levels(mMall)[2:6] ) )
> T3 <- update( T0, . ~ - Ixgr + I( lex.Cst %in% levels(mMall)[2:6] ) +
+           I( lex.Cst %in% levels(mMall)[2:6] ):Ixgr )
> round( ci.exp( T0 ), 3 )
              exp(Est.)  2.5% 97.5%
(Intercept)      0.046 0.044 0.049
IxgrSGLT2        0.495 0.427 0.572

> round( ci.exp( T1 ), 3 )
              exp(Est.)  2.5%      97.5%
(Intercept)      0.040  0.038 4.300000e-02
IxgrSGLT2        0.511  0.442 5.920000e-01
factor(lex.Cst)1 HF      16.449 13.886 1.948500e+01
factor(lex.Cst)2 HF      17.707 12.654 2.477700e+01
factor(lex.Cst)3 HF      29.109 15.622 5.423900e+01
factor(lex.Cst)4 HF      31.466 13.071 7.575200e+01
factor(lex.Cst)5+ HF      0.000  0.000 2.605356e+93

> round( ci.exp( T2 ), 3 )
              exp(Est.)  2.5% 97.5%
(Intercept)      0.040  0.038  0.043
IxgrSGLT2        0.511  0.441  0.591
I(lex.Cst %in% levels(mMall)[2:6])TRUE      17.054 14.689 19.801

> round( ci.exp( T3 ), 3 )
              exp(Est.)  2.5% 97.5%
(Intercept)      0.040  0.038  0.043
I(lex.Cst %in% levels(mMall)[2:6])TRUE      16.899 14.402 19.828
I(lex.Cst %in% levels(mMall)[2:6])FALSE:IxgrSGLT2      0.506  0.433  0.592
I(lex.Cst %in% levels(mMall)[2:6])TRUE:IxgrSGLT2      0.545  0.358  0.828

> anova( T0, T1, T2, T3, test="Chisq" )
Analysis of Deviance Table

Model 1: (lex.Xst %in% levels(mMall)[2:7] & lex.Xst != lex.Cst) ~ Ixgr
Model 2: (lex.Xst %in% levels(mMall)[2:7] & lex.Xst != lex.Cst) ~ Ixgr +
  factor(lex.Cst)
Model 3: (lex.Xst %in% levels(mMall)[2:7] & lex.Xst != lex.Cst) ~ Ixgr +
  I(lex.Cst %in% levels(mMall)[2:6])
Model 4: (lex.Xst %in% levels(mMall)[2:7] & lex.Xst != lex.Cst) ~ I(lex.Cst %in%
  levels(mMall)[2:6]) + I(lex.Cst %in% levels(mMall)[2:6]):Ixgr
  Resid. Df Resid. Dev Df Deviance Pr(>Chi)
1      33341      12289
2      33336      11549  5    739.66 < 2e-16 ***
3      33340      11558 -4    -8.59  0.07206 .
4      33339      11558  1     0.10  0.74964
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

Including death as a part of the endpoint produces a smaller HR for SGLT2, and one that is not so confounded by HF status, mainly because the deaths prior to HF will dominate the analysis totally. As illustration we can compare the results for analysis of death alone (for the total follow-up):

```
> X0 <- glm( ( lex.Xst %in% levels(mMall)[7] & lex.Xst!=lex.Cst ) ~ Ixgr,
+           offset = log( lex.dur ),
+           family = poisson,
+           data = mMall )
> X1 <- update( X0, . ~ . + factor( lex.Cst ) )
> X2 <- update( X0, . ~ . + I( lex.Cst %in% levels(mMall)[2:6] ) )
> X3 <- update( X0, . ~ - Ixgr + I( lex.Cst %in% levels(mMall)[2:6] ) +
+           I( lex.Cst %in% levels(mMall)[2:6] ):Ixgr )
> round( cbind( ci.exp( X0 ), ci.exp( T0 ) ), 3 )
```

	exp(Est.)	2.5%	97.5%	exp(Est.)	2.5%	97.5%
(Intercept)	0.029	0.027	0.032	0.046	0.044	0.049
IxgrSGLT2	0.409	0.335	0.499	0.495	0.427	0.572

```
> round( cbind( ci.exp( X1 ), ci.exp( T1 ) ), 3 )
```

	exp(Est.)	2.5%	97.5%	exp(Est.)	2.5%	97.5%
(Intercept)	0.028	0.026	3.000000e-02	0.040	0.038	4.300000e-02
IxgrSGLT2	0.414	0.340	5.060000e-01	0.511	0.442	5.920000e-01
factor(lex.Cst)1 HF	7.135	5.269	9.661000e+00	16.449	13.886	1.948500e+01
factor(lex.Cst)2 HF	8.929	5.050	1.578700e+01	17.707	12.654	2.477700e+01
factor(lex.Cst)3 HF	0.000	0.000	3.308567e+158	29.109	15.622	5.423900e+01
factor(lex.Cst)4 HF	9.081	1.278	6.455200e+01	31.466	13.071	7.575200e+01
factor(lex.Cst)5+ HF	0.000	0.000	3.216054e+259	0.000	0.000	2.605356e+93

```
> round( cbind( ci.exp( X2 ), ci.exp( T2 ) ), 3 )
```

	exp(Est.)	2.5%	97.5%	exp(Est.)	2.5%	97.5%
(Intercept)	0.028	0.026	0.030	0.040	0.038	0.043
IxgrSGLT2	0.415	0.340	0.506	0.511	0.441	0.591
I(lex.Cst %in% levels(mMall)[2:6])TRUE	7.175	5.486	9.383	17.054	14.689	19.801

```
> round( cbind( ci.exp( X3 ), ci.exp( T3 ) ), 3 )
```

	exp(Est.)	2.5%	97.5%	exp(Est.)	2.5%	97.5%
(Intercept)	0.028	0.026	0.030	0.040	0.038	0.043
I(lex.Cst %in% levels(mMall)[2:6])TRUE	7.263	5.482	9.622	16.899	14.402	
I(lex.Cst %in% levels(mMall)[2:6])FALSE:IxgrSGLT2	0.417	0.340	0.512	0.506	0.433	
I(lex.Cst %in% levels(mMall)[2:6])TRUE:IxgrSGLT2	0.367	0.146	0.918	0.545	0.358	

	exp(Est.)	2.5%	97.5%
(Intercept)	0.043		
I(lex.Cst %in% levels(mMall)[2:6])TRUE	19.828		
I(lex.Cst %in% levels(mMall)[2:6])FALSE:IxgrSGLT2	0.592		
I(lex.Cst %in% levels(mMall)[2:6])TRUE:IxgrSGLT2	0.828		

1.1.5 Saving results

When saving the results, we use the convention that “m” refer to models for follow-up on drug only, “t” to total follow-up, and lower case letters to models with only HF’s counted as events, while upper case letters refer to models with HF and death as combined endpoints.

```
> m0 <- ci.lin( m0 )
> m1 <- ci.lin( m1 )
> m2 <- ci.lin( m2 )
> t0 <- ci.lin( t0 )
> t1 <- ci.lin( t1 )
> t2 <- ci.lin( t2 )
> M0 <- ci.lin( M0 )
> M1 <- ci.lin( M1 )
> M2 <- ci.lin( M2 )
> T0 <- ci.lin( T0 )
> T1 <- ci.lin( T1 )
> T2 <- ci.lin( T2 )
> save( onDrFU, allFU,
+       m0, m1, m2, t0, t1, t2,
+       M0, M1, M2, T0, T1, T2,
+       file="MTrecHF.Rda" )
```