

# CVD mortality and plasma apolipoproteine A1

19. januar 2016

# Population

# WECAC

Patients included in the WECAC cohort underwent coronary angiography between January 2000 and April 2004 at either Bergen University Hospital or Stavanger University Hospital; some of the patients were subsequently included in the Western Norway B Vitamin Intervention Trial (clinicaltrials.gov identifier NCT00364081). Patients were followed up for ICD10 readmission diagnoses in patient administrative registries in any Norwegian Hospital until end of 2009 and for ICD10 cause of death diagnoses until end of 2012.

Only patients with baseline measurements, stable angina pectoris were included.

# Main Endpoint

# CVD mortality

CVD mortality is observed in 417 of 4166 patients (10%) with a median follow-up time of 3758 days. Acknowledgment: The authors thank Tomislav Dimoski at The Norwegian Knowledge Centre for the Health Services, Oslo, Norway for his contribution by developing the software necessary for obtaining data from Norwegian hospitals, conducting the data collection and quality assurance of data in this project.

# Survival

# CVD mortality $\sim$ apo A1

	Unadjusted			Adjustment 1			Adjustment 2		
	HR	CI	P	HR	CI	P	HR	CI	P
zApA1	0.89	(0.81,0.99)	0.026	0.86	(0.77,0.96)	0.005	0.87	(0.79,0.97)	0.012
zlogApA1	0.88	(0.80,0.96)	0.007	0.84	(0.76,0.93)	0.001	0.86	(0.78,0.95)	0.003
trend4ApA1	0.86	(0.79,0.94)	0.001	0.84	(0.76,0.92)	<0.001	0.85	(0.78,0.93)	<0.001

**Tabell :** Hazard ratios for association between CVD mortality and plasma apolipoproteine A1 estimated with Cox proportional hazards models; adjustment 1 for age, sex; adjustment 2 additionally for diabetes mellitus, current smoking, hypertension.

# Interaction



## CVD mortality and apo A1 in subgroups of high/low choline

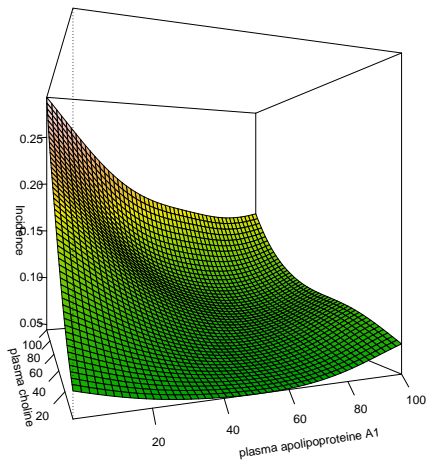
	Low plasma choline		High plasma choline		Interaction
	HR	CI	HR	CI	P-value
<b>Unadjusted</b>					
zApA1	1.01	(0.86,1.19)	0.78	(0.69,0.89)	0.015
zlogApA1	0.97	(0.82,1.14)	0.78	(0.69,0.88)	0.030
trend4ApA1	0.95	(0.82,1.10)	0.78	(0.70,0.87)	0.030
<b>Adjustment 1</b>					
zApA1	0.99	(0.83,1.17)	0.77	(0.67,0.88)	0.067
zlogApA1	0.95	(0.80,1.12)	0.76	(0.67,0.86)	0.086
trend4ApA1	0.93	(0.79,1.08)	0.77	(0.69,0.86)	0.128
<b>Adjustment 2</b>					
zApA1	0.99	(0.83,1.18)	0.79	(0.69,0.90)	0.081
zlogApA1	0.96	(0.81,1.13)	0.78	(0.69,0.89)	0.107
trend4ApA1	0.94	(0.80,1.09)	0.79	(0.70,0.88)	0.133

**Tabell :** Hazard ratios for association between CVD mortality and plasma apolipoprotein A1 in subgroups of high vs. low levels of plasma choline estimated with Cox proportional hazards models; adjustment 1 for age, sex; adjustment 2 additionally for diabetes mellitus, current smoking, hypertension. The effect modifier plasma choline is divided into high/low levels according to the population median of 9.66.

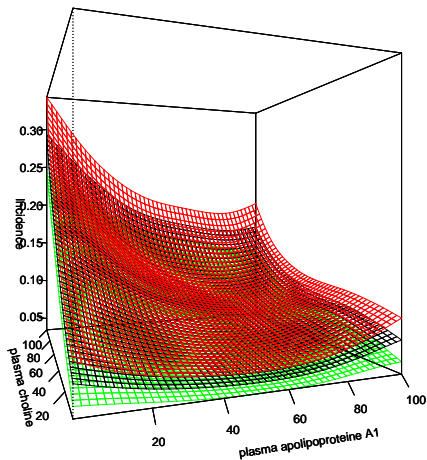
# CVD mortality and apo A1 and interaction with high/low choline

	Unadjusted			Adjustment 1			Adjustment 2		
	HR	CI	P	HR	CI	P	HR	CI	P
<b>Normalized</b>									
zApA1	1.01	(0.86,1.19)	0.900	0.95	(0.80,1.12)	0.543	0.96	(0.81,1.14)	0.657
dcholine(9.66,34.8]	1.90	(1.55,2.33)	<0.001	1.33	(1.08,1.64)	0.007	1.32	(1.07,1.62)	0.010
zApA1:dcholine(9.66,34.8]	0.77	(0.63,0.95)	0.015	0.82	(0.67,1.01)	0.067	0.83	(0.68,1.02)	0.081
<b>Normalized log</b>									
zlogApA1	0.97	(0.82,1.14)	0.711	0.92	(0.78,1.08)	0.302	0.93	(0.79,1.09)	0.389
dcholine(9.66,34.8]	1.91	(1.56,2.34)	<0.001	1.34	(1.09,1.65)	0.006	1.32	(1.07,1.63)	0.009
zlogApA1:dcholine(9.66,34.8]	0.80	(0.65,0.98)	0.030	0.84	(0.69,1.02)	0.086	0.85	(0.70,1.04)	0.107
<b>Trend over quartiles</b>									
trend4ApA1	0.95	(0.82,1.10)	0.503	0.90	(0.78,1.04)	0.164	0.91	(0.79,1.06)	0.239
dcholine(9.66,34.8]	3.15	(1.97,5.03)	<0.001	1.89	(1.18,3.03)	0.008	1.86	(1.16,2.98)	0.010
trend4ApA1:dcholine(9.66,34.8]	0.82	(0.68,0.98)	0.030	0.87	(0.72,1.04)	0.128	0.87	(0.73,1.04)	0.133

**Tabell :** Hazard ratios for association between CVD mortality and plasma apolipoproteine A1 and effect modification by high vs low levels of plasma choline (divided into high/low levels according to the population median of 9.66) estimated with Cox proportional hazards models; adjustment 1 for age, sex; adjustment 2 additionally for diabetes mellitus, current smoking, hypertension.



Surface spline of CVD mortality incidence by empirical percentiles of plasma apolipoprotein A1 and plasma choline estimated with a Generalized Additive Model.



red/green are  $\pm$  TRUE s.e.

Surface spline of CVD mortality incidence by empirical percentiles of plasma apolipoprotein A1 and plasma choline estimated with a Generalized Additive Model; coloured grids depict 95% confidence levels.

# Appendix

...containing the crude complete output of all models

# Normalized

```
## Call:
## coxph(formula = BuildCoxFormula(alevel = 0, ptrans = "z"), data = D)
##
##
##          coef exp(coef) se(coef)      z      p
## zApA1 -0.113      0.893    0.051 -2.22 0.026
##
## Likelihood ratio test=5.02  on 1 df, p=0.025
## n= 4163, number of events= 416
## (3 observations deleted due to missingness)
```

# Normalized

```
## Call:
## coxph(formula = BuildCoxFormula(alevel = 1, ptrans = "z"), data = D)
##
##
##           coef exp(coef) se(coef)      z      p
## zApA1    -0.1516   0.8593   0.0541 -2.80 0.0051
## age       0.0942   1.0988   0.0058 16.25 <2e-16
## sexmale   0.3821   1.4654   0.1221  3.13 0.0018
##
## Likelihood ratio test=313  on 3 df, p=0
## n= 4163, number of events= 416
## (3 observations deleted due to missingness)
```

# Normalized

```
## Call:
## coxph(formula = BuildCoxFormula(alevel = 2, ptrans = "z"), data = D)
##
##
##               coef exp(coef) se(coef)      z      p
## zApA1          -0.13529   0.87346  0.05373 -2.52 0.0118
## age             0.10168   1.10703  0.00622 16.36 < 2e-16
## sexmale         0.32440   1.38320  0.13185  2.46  0.0139
## diabetes_mellitustype I    1.19710   3.31049  0.50707  2.36  0.0182
## diabetes_mellitustype II   0.53705   1.71095  0.12517  4.29 1.8e-05
## smoking_habitsex-smoker < 1 month 0.49292   1.63709  0.34370  1.43  0.1515
## smoking_habitsnever smoked -0.23862   0.78771  0.13241 -1.80  0.0715
## smoking_habitssmoker      0.64473   1.90547  0.12795  5.04 4.7e-07
## hypertensionyes          0.32834   1.38867  0.10319  3.18  0.0015
##
## Likelihood ratio test=383 on 9 df, p=0
## n= 4156, number of events= 415
## (10 observations deleted due to missingness)
```



# Normalized log

```
## Call:
## coxph(formula = BuildCoxFormula(alevel = 0, ptrans = "zlog"),
##       data = D)
##
##
##               coef exp(coef) se(coef)      z      p
## zlogApA1 -0.1318    0.8765   0.0488 -2.7 0.007
##
## Likelihood ratio test=7.17 on 1 df, p=0.00739
## n= 4163, number of events= 416
## (3 observations deleted due to missingness)
```

# Normalized log

```
## Call:
## coxph(formula = BuildCoxFormula(alevel = 1, ptrans = "zlog"),
##       data = D)
##
##
##               coef exp(coef) se(coef)      z      p
## zlogApA1 -0.1686    0.8449   0.0508 -3.32 0.00091
## age      0.0943    1.0989   0.0058 16.27 < 2e-16
## sexmale  0.3714    1.4498   0.1217  3.05 0.00227
##
## Likelihood ratio test=316 on 3 df, p=0
## n= 4163, number of events= 416
## (3 observations deleted due to missingness)
```

# Normalized log

```
## Call:
## coxph(formula = BuildCoxFormula(alevel = 2, ptrans = "zlog"),
##       data = D)
##
##
##               coef exp(coef) se(coef)      z      p
## zlogApA1        -0.15184   0.85912  0.05091 -2.98 0.0029
## age             0.10180   1.10716  0.00622 16.38 < 2e-16
## sexmale         0.31234   1.36662  0.13154  2.37  0.0176
## diabetes_mellitustype I 1.20626   3.34097  0.50709  2.38  0.0174
## diabetes_mellitustype II 0.53064   1.70001  0.12518  4.24 2.2e-05
## smoking_habitsex-smoker < 1 month 0.49544   1.64122  0.34370  1.44  0.1494
## smoking_habitsnever smoked -0.24203   0.78503  0.13237 -1.83  0.0675
## smoking_habitsmoker      0.63973   1.89597  0.12797  5.00 5.8e-07
## hypertensionyes         0.32865   1.38910  0.10318  3.19  0.0014
##
## Likelihood ratio test=385 on 9 df, p=0
## n= 4156, number of events= 415
## (10 observations deleted due to missingness)
```

# Trend over quartiles

```
## Call:
## coxph(formula = BuildCoxFormula(alevel = 0, ptrans = "trend4"),
##       data = D)
##
##
##               coef exp(coef) se(coef)      z      p
## trend4ApA1 -0.1464    0.8638   0.0445 -3.29 0.001
##
## Likelihood ratio test=10.9 on 1 df, p=0.000961
## n= 4163, number of events= 416
## (3 observations deleted due to missingness)
```

# Trend over quartiles

```
## Call:
## coxph(formula = BuildCoxFormula(alevel = 1, ptrans = "trend4"),
##       data = D)
##
##
##               coef exp(coef) se(coef)      z      p
## trend4ApA1 -0.17825   0.83673  0.04631 -3.85 0.00012
## age         0.09431   1.09890  0.00579 16.30 < 2e-16
## sexmale     0.35465   1.42569  0.12143  2.92 0.00349
##
## Likelihood ratio test=320 on 3 df, p=0
## n= 4163, number of events= 416
## (3 observations deleted due to missingness)
```

# Trend over quartiles

```
## Call:
## coxph(formula = BuildCoxFormula(alevel = 2, ptrans = "trend4"),
##       data = D)
##
##
##
##               coef exp(coef) se(coef)      z      p
## trend4ApA1      -0.16362   0.84906  0.04637 -3.53 0.00042
## age              0.10182   1.10719  0.00621 16.40 < 2e-16
## sexmale          0.29925   1.34884  0.13083  2.29 0.02218
## diabetes_mellitustype I 1.20735   3.34462  0.50694  2.38 0.01724
## diabetes_mellitustype II 0.52300   1.68708  0.12527  4.18 3.0e-05
## smoking_habitsex-smoker < 1 month 0.49392   1.63873  0.34367  1.44 0.15066
## smoking_habitsnever smoked -0.24070   0.78607  0.13227 -1.82 0.06878
## smoking_habitsssmoker   0.64075   1.89789  0.12810  5.00 5.7e-07
## hypertensionyes        0.33332   1.39560  0.10327  3.23 0.00125
##
## Likelihood ratio test=389 on 9 df, p=0
## n= 4156, number of events= 415
## (10 observations deleted due to missingness)
```

# Normalized

```
## Call:
## coxph(formula = BuildCoxFormula(alevel = 0, mtrans = "d", ptrans = "z"),
##       data = D)
##
##
##               coef exp(coef) se(coef)      z      p
## zApA1           0.0106    1.0107  0.0846  0.13  0.900
## dcholine(9.66,34.8] 0.6438    1.9038  0.1034  6.23 4.7e-10
## zApA1:dcholine(9.66,34.8] -0.2598    0.7712  0.1072 -2.42  0.015
##
## Likelihood ratio test=56.2 on 3 df, p=3.73e-12
## n= 4154, number of events= 414
## (12 observations deleted due to missingness)
```

# Normalized

```
## Call:
## coxph(formula = BuildCoxFormula(alevel = 1, mtrans = "d", ptrans = "z"),
##       data = D)
##
##
##               coef exp(coef) se(coef)      z      p
## zApA1          -0.05207   0.94926  0.08553 -0.61 0.5427
## dcholine(9.66,34.8]  0.28668   1.33200  0.10632  2.70 0.0070
## age              0.08987   1.09403  0.00591 15.20 <2e-16
## sexmale           0.33460   1.39739  0.12452  2.69 0.0072
## zApA1:dcholine(9.66,34.8] -0.19525   0.82263  0.10661 -1.83 0.0670
##
## Likelihood ratio test=321  on 5 df, p=0
## n= 4154, number of events= 414
## (12 observations deleted due to missingness)
```



# Normalized

```
## Call:
## coxph(formula = BuildCoxFormula(alevel = 2, mtrans = "d", ptrans = "z"),
##       data = D)
##
##
##               coef exp(coef) se(coef)      z      p
## zApA1          -0.03799   0.96273  0.08548 -0.44  0.6568
## dcholine(9.66,34.8]  0.27526   1.31687  0.10703  2.57  0.0101
## age             0.09786   1.10281  0.00631 15.52 < 2e-16
## sexmale         0.28676   1.33211  0.13346  2.15  0.0317
## diabetes_mellitustype I  1.14964   3.15706  0.50730  2.27  0.0234
## diabetes_mellitustype II 0.54290   1.72099  0.12551  4.33 1.5e-05
## smoking_habitsex-smoker < 1 month 0.49563   1.64154  0.34369  1.44  0.1493
## smoking_habitsnever smoked -0.22556   0.79807  0.13244 -1.70  0.0886
## smoking_habitssmoker    0.67670   1.96737  0.12857  5.26 1.4e-07
## hypertensionyes       0.30212   1.35272  0.10362  2.92  0.0035
## zApA1:dcholine(9.66,34.8] -0.18443   0.83158  0.10578 -1.74  0.0812
##
## Likelihood ratio test=390  on 11 df, p=0
## n= 4147, number of events= 413
## (19 observations deleted due to missingness)
```

# Normalized log

```
## Call:
## coxph(formula = BuildCoxFormula(alevel = 0, mtrans = "d", ptrans = "zlog"),
##       data = D)
##
##
##               coef exp(coef) se(coef)      z      p
## zlogApA1        -0.0306   0.9698   0.0827 -0.37   0.71
## dcholine(9.66,34.8]  0.6484   1.9125   0.1036  6.26 3.9e-10
## zlogApA1:dcholine(9.66,34.8] -0.2225   0.8006   0.1027 -2.17   0.03
##
## Likelihood ratio test=58.1 on 3 df, p=1.52e-12
## n= 4154, number of events= 414
## (12 observations deleted due to missingness)
```

# Normalized log

```
## Call:
## coxph(formula = BuildCoxFormula(alevel = 1, mtrans = "d", ptrans = "zlog"),
##       data = D)
##
##
##               coef exp(coef) se(coef)      z      p
## zlogApA1        -0.08410   0.91934  0.08147  -1.03 0.3019
## dcholine(9.66,34.8]  0.29182   1.33886  0.10655   2.74 0.0062
## age              0.09004   1.09422  0.00591  15.23 <2e-16
## sexmale          0.32213   1.38006  0.12389   2.60 0.0093
## zlogApA1:dcholine(9.66,34.8] -0.17320   0.84097  0.10095  -1.72 0.0862
##
## Likelihood ratio test=324 on 5 df, p=0
## n= 4154, number of events= 414
## (12 observations deleted due to missingness)
```

# Normalized log

```
## Call:
## coxph(formula = BuildCoxFormula(alevel = 2, mtrans = "d", ptrans = "zlog"),
##       data = D)
##
##
##               coef exp(coef) se(coef)      z      p
## zlogApA1        -0.07023   0.93218  0.08159 -0.86  0.3894
## dcholine(9.66,34.8]  0.27958   1.32257  0.10725  2.61  0.0091
## age              0.09805   1.10302  0.00631 15.55 < 2e-16
## sexmale          0.27178   1.31230  0.13300  2.04  0.0410
## diabetes_mellitustype I  1.16310   3.19983  0.50730  2.29  0.0219
## diabetes_mellitustype II 0.53318   1.70434  0.12556  4.25 2.2e-05
## smoking_habitsex-smoker < 1 month 0.49997   1.64868  0.34371  1.45  0.1458
## smoking_habitsnever smoked -0.23056   0.79409  0.13239 -1.74  0.0816
## smoking_habitssmoker    0.67119   1.95657  0.12854  5.22 1.8e-07
## hypertensionyes       0.30108   1.35131  0.10360  2.91  0.0037
## zlogApA1:dcholine(9.66,34.8] -0.16228   0.85020  0.10067 -1.61  0.1070
##
## Likelihood ratio test=392 on 11 df, p=0
## n= 4147, number of events= 413
## (19 observations deleted due to missingness)
```

# Trend over quartiles

```
## Call:
## coxph(formula = BuildCoxFormula(alevel = 0, mtrans = "d", ptrans = "trend4"),
##       data = D)
##
##
##               coef exp(coef) se(coef)      z      p
## trend4ApA1      -0.0500   0.9512  0.0746 -0.67   0.50
## dcholine(9.66,34.8]  1.1462   3.1462  0.2397  4.78 1.7e-06
## trend4ApA1:dcholine(9.66,34.8] -0.2028   0.8164  0.0934 -2.17   0.03
##
## Likelihood ratio test=62.3 on 3 df, p=1.93e-13
## n= 4154, number of events= 414
## (12 observations deleted due to missingness)
```

# Trend over quartiles

```
## Call:
## coxph(formula = BuildCoxFormula(alevel = 1, mtrans = "d", ptrans = "trend4"),
##       data = D)
##
##
##               coef exp(coef) se(coef)      z      p
## trend4ApA1      -0.1051   0.9002   0.0756 -1.39 0.1641
## dcholine(9.66,34.8]  0.6388   1.8941   0.2395  2.67 0.0077
## age              0.0898   1.0940   0.0059 15.22 <2e-16
## sexmale          0.3050   1.3566   0.1237  2.47 0.0137
## trend4ApA1:dcholine(9.66,34.8] -0.1409   0.8686   0.0926 -1.52 0.1282
##
## Likelihood ratio test=328 on 5 df, p=0
## n= 4154, number of events= 414
## (12 observations deleted due to missingness)
```

# Trend over quartiles

```
## Call:
## coxph(formula = BuildCoxFormula(alevel = 2, mtrans = "d", ptrans = "trend4"),
##       data = D)
##
##
##               coef exp(coef) se(coef)      z      p
## trend4ApA1      -0.0891   0.9147   0.0756 -1.18  0.2387
## dcholine(9.66,34.8]  0.6212   1.8611   0.2397  2.59  0.0095
## age              0.0979   1.1028   0.0063 15.53 < 2e-16
## sexmale          0.2615   1.2989   0.1322  1.98  0.0479
## diabetes_mellitustype I  1.1586   3.1856   0.5072  2.28  0.0224
## diabetes_mellitustype II 0.5337   1.7053   0.1255  4.25 2.1e-05
## smoking_habitsex-smoker < 1 month 0.4999   1.6486   0.3437  1.45  0.1458
## smoking_habitsnever smoked -0.2258   0.7978   0.1323 -1.71  0.0877
## smoking_habitssmoker    0.6724   1.9589   0.1287  5.22 1.7e-07
## hypertensioyes        0.3078   1.3604   0.1037  2.97  0.0030
## trend4ApA1:dcholine(9.66,34.8] -0.1390   0.8702   0.0926 -1.50  0.1333
##
## Likelihood ratio test=396 on 11 df, p=0
## n= 4147, number of events= 413
## (19 observations deleted due to missingness)
```