

Repeated Measurement (short)

- Hypertension
 - Study design
 - Data
 - Within Subject Effect (time)
 - Values
 - Means
 - Tests
 - Multivariate Test Results
 - Univariate Mauchly's Sphericity -Test and ϵ correction
 - Univariate Corrected Test Results
 - Other Effects
 - Univariate Test Results
 - Marginal Mean Plots
 - Mean Confidence Plots and Résumé

Hypertension: Study Design Panel Study

Prospective randomized balanced cohort study

Population	Patients with high blood pressure: systolic ≥ 135
Sampling Design	A stratified (gender equal proportion) sample was drawn randomly from the population (360 patients)
Experimental Design	Patients were randomly balanced allocated to 3 Therapies (Alphasan, Betasan, Standard) So that each 60 men and 60 women from the sample received one therapy.
Variables	Basic variables of patients were recorded at start. Blood pressure (systolic and diastolic), Cholesterol und Bloodsugar were recorded at start and after 1, 6 and 12 months.

Hypertension: Data

	patid	gender	therapy	age	ageclass	height	weight	bmi	bmi	rs0	rs1	rs6	rs12	rd0	rd1	rd6	rd12	chol0	chol1	chol6	chol12	bs0	bs1	bs6	bs12	rsdif	rddif
1	97	mal	Alphasa	68	66-7	175	76	24,82	Normweigh	151	144	126	124	102	93	70	70	331	298	355	375	80	85	90	90	-27,0	-32,00
2	141	mal	Alphasa	53	<=55	171	76	25,99	Normweigh	147	139	118	115	103	90	70	70	220	235	240	245	86	78	92	93	-32,0	-33,00
3	179	mal	Alphasa	71	66-7	158	62	24,84	Normweigh	152	147	128	125	108	96	71	70	180	175	175	195	105	100	93	95	-27,0	-38,00
4	270	mal	Alphasa	61	56-6	170	85	29,41	Overweigh	149	144	125	123	106	92	73	70	288	300	301	310	137	124	100	99	-26,0	-36,00
5	334	mal	Alphasa	52	<=55	176	78	25,18	Normweigh	146	139	119	115	101	86	70	70	185	180	195	170	87	82	78	80	-31,0	-31,00
6	34	mal	Alphasa	71	66-7	165	57	20,94	Underweig	150	144	126	123	110	92	70	70	331	350	431	401	135	180	200	175	-27,0	-40,00
7	4	mal	Alphasa	53	<=55	174	83	27,41	Overweigh	146	139	121	118	100	90	70	70	220	220	235	200	105	100	91	100	-28,0	-30,00
8	152	mal	Alphasa	53	<=55	170	68	23,53	Normweigh	143	136	117	113	99	85	70	70	202	199	221	201	97	88	93	97	-30,0	-29,00
9	69	mal	Alphasa	53	<=55	168	65	23,03	Normweigh	146	138	120	117	100	90	70	70	172	245	211	190	87	95	99	94	-29,0	-30,00
10	321	mal	Alphasa	69	66-7	171	70	23,94	Underweig	151	146	127	124	105	93	70	70	317	300	289	275	92	106	90	97	-27,0	-35,00
11	302	mal	Alphasa	52	<=55	176	80	25,83	Normweigh	147	141	125	120	106	91	70	70	240	250	253	210	71	75	88	70	-27,0	-36,00

If we think of time as an effect, then it would be something like the correlations of rrs0, rrs1, rrs6, rrs12 (*) (the systolic blood pressure at start, 1, 6, 12 months after start) for different gender and therapy groups.

(*) here we concentrate on the systolic blood pressure at start, and 1, 6, 12 months after start (rrs0, rrs1, rrs6, rrs12)

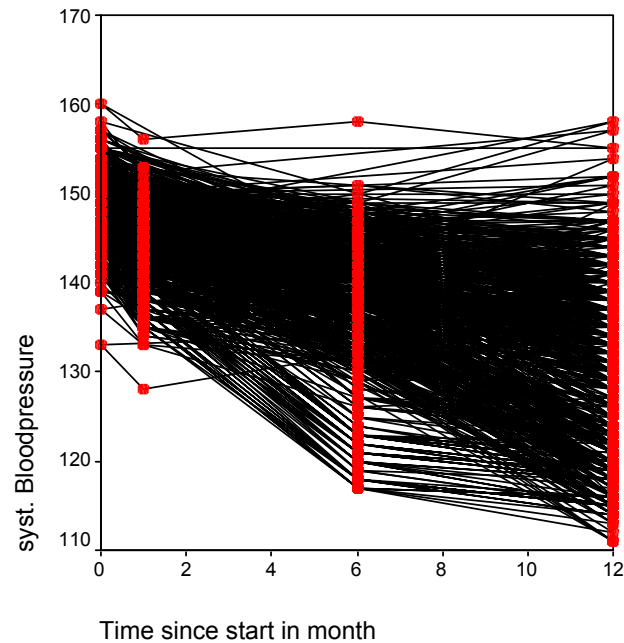


Hypertension: Within Subject Effect (time) Values

We will now concentrate on the analysis of the systolic blood pressure over time.

For every patient we have 4 measurements within 12 months

Here you can see the individual development of systolic blood pressure for the 360 patients



This time influence is called the within subjects effect

Hypertension: Within Subject Effect (time) Means

If we look at the mean value at every time point we can see the influence of time more easily

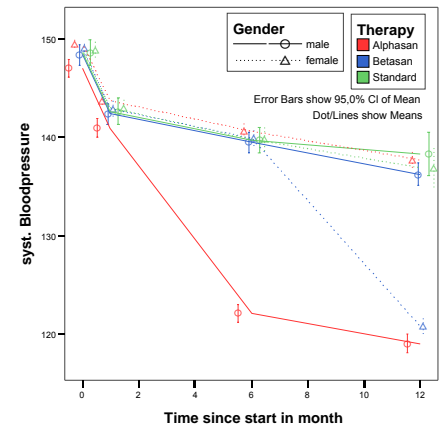
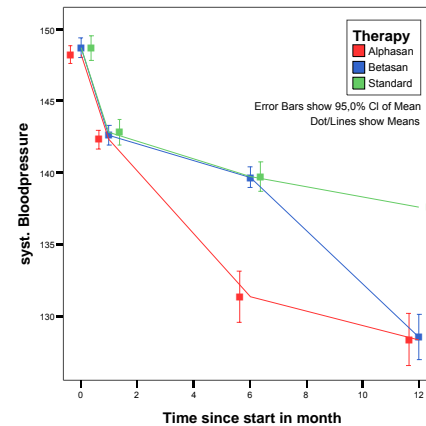
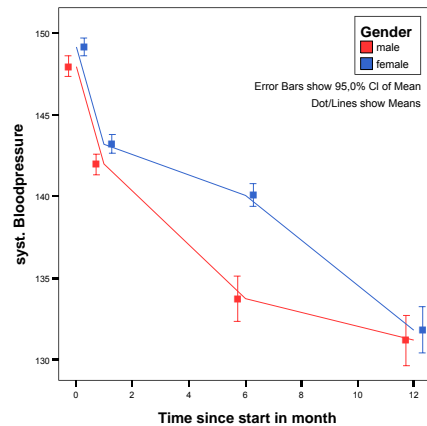
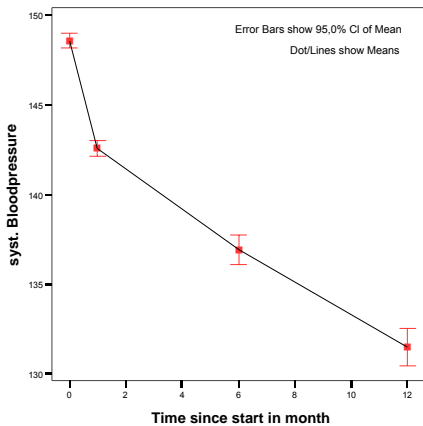
Time influence could be

general

different among gender

different among therapies

different among therapies x gender



Hypertension: Within Subject Effect (time) Tests

Multivariate

$$\begin{pmatrix} rrs_0 \\ rrs_1 \\ rrs_6 \\ rrs_{12} \end{pmatrix} = \begin{pmatrix} \mu_0 \\ \mu_1 \\ \mu_6 \\ \mu_{12} \end{pmatrix} + \begin{pmatrix} \text{gender} \\ \text{gender} \\ \text{gender} \\ \text{gender} \end{pmatrix} + \begin{pmatrix} \text{therapy} \\ \text{therapy} \\ \text{therapy} \\ \text{therapy} \end{pmatrix} + \begin{pmatrix} \text{gender} \times \text{therapy} \\ \text{gender} \times \text{therapy} \\ \text{gender} \times \text{therapy} \\ \text{gender} \times \text{therapy} \end{pmatrix} + \begin{pmatrix} \varepsilon_0 \\ \varepsilon_1 \\ \varepsilon_6 \\ \varepsilon_{12} \end{pmatrix}$$

Assumptions:

- The error term is *multivariate* normal distributed
- with equal variances for different groups

Box's Test equal variances across groups
(volatile against deviation from multivariate normality)

General warning: testing assumptions will lead to known problems (see basics)

4 Tests to test time influence

Pillai's Trace most robust and powerful
Wilks' Lambda
Hotelling's Trace
Roy's Largest Root

Univariate

$$\frac{rrs0 + rrs1 + rrs6 + rrs12}{\sqrt{4}} = \mu + \text{gender} + \text{therapy} + \text{time} + \text{interactions} + e$$

Assumptions:

- The error term is normal distributed
- the covariance matrix of e is tolerable

Mauchly's Sphericity-Test: covariance of e for orthonormalized dependent (over groups) has H-Form (Huynh-Feldt) = proportional to identity. Gives correct factor ε for the next 4 tests

4 Tests to test time influence
depending on correcting factor $\varepsilon < 1$

Sphericity assumed
Greenhouse-Geisser conservative for small samples
Huynh-Feldt not so conservative but tends to overcorrect $\varepsilon > 1$
Lower bound most conservative, assumes most possible departure from Sphericity



Syntax

SPSS 13

GLM

```
rrs0 rrs1 rrs6 rrs12 BY therapy gender  
/WSFACTOR = time 4 Polynomial  
/POSTHOC = therapy gender ( TUKEY )  
/PLOT = PROFILE( time*therapy*gender )  
/PRINT = DESCRIPTIVE ETASQ  
/WSDESIGN = time  
/DESIGN = therapy gender therapy*gender .
```

SAS 9.2:

```
proc glm;  
    class gender therapy;  
    model rrs0 rrs1 rrs6 rrs12 = gender | therapy;  
    repeated time 4 (0 1 6 12) polynomial / summary printe;  
run;
```

time can – in contrary to SPSS – have other than equidistant measures.

In both cases "time" is a dummy variable which could have any name (just for the output)



Hypertension: Within Subject Effect (time)

Multivariate Test Results

Now following the 4 multivariate tests of the time effect (within subject) of which **Pillai's trace** is known to be the most robust and powerful one.

Multivariate Tests^c

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
TIME	Pillai's Trace	,978	5307,745 ^a	3,000	352,000	,000	,978
	Wilks' Lambda	,022	5307,745 ^a	3,000	352,000	,000	,978
	Hotelling's Trace	45,236	5307,745 ^a	3,000	352,000	,000	,978
	Roy's Largest Root	45,236	5307,745 ^a	3,000	352,000	,000	,978
TIME * GENDER	Pillai's Trace	,679	247,902 ^a	3,000	352,000	,000	,679
	Wilks' Lambda	,321	247,902 ^a	3,000	352,000	,000	,679
	Hotelling's Trace	2,113	247,902 ^a	3,000	352,000	,000	,679
	Roy's Largest Root	2,113	247,902 ^a	3,000	352,000	,000	,679
TIME * THERAPY	Pillai's Trace	1,241	192,391	6,000	706,000	,000	,621
	Wilks' Lambda	,114	229,859 ^a	6,000	704,000	,000	,662
	Hotelling's Trace	4,646	271,770	6,000	702,000	,000	,699
	Roy's Largest Root	3,835	451,199 ^b	3,000	353,000	,000	,793
TIME * GENDER * THERAPY	Pillai's Trace	1,139	155,806	6,000	706,000	,000	,570
	Wilks' Lambda	,130	207,834 ^a	6,000	704,000	,000	,639
	Hotelling's Trace	4,609	269,630	6,000	702,000	,000	,697
	Roy's Largest Root	4,104	482,958 ^b	3,000	353,000	,000	,804

a. Exact statistic

b. The statistic is an upper bound on F that yields a lower bound on the significance level.

c.

Design: Intercept+GENDER+THERAPY+GENDER * THERAPY

Within Subjects Design: TIME



Hypertension: Within Subject Effect (time)

Univariate Mauchly's Sphericity –Test and ϵ correction

This is a "pretest" which tests one of the assumptions for later univariate tests (Caution ! see basics)

Mauchly's Test of Sphericity^b

Measure: MEASURE_1

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon ^a		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound
TIME	,103	800,961	5	,000	,482	,490	,333

Tests the null hypothesis that the error covariance matrix of the orthonormalized transformed dependent variables is proportional to an identity matrix.

a. May be used to adjust the degrees of freedom for the averaged tests of significance. Corrected tests are displayed in the Tests of Within-Subjects Effects table.

b.

Design: Intercept+GENDER+THERAPY+GENDER * THERAPY

Within Subjects Design: TIME

Mauchly's Sphericity-Test: tests whether the covariance matrix of e for orthonormalized dependent variables (rrs0, rrs1, rrs6, rrs12) over groups has at least a tolerable form (Huynh-Feldt-Form = H-Form)

which means that it is proportional to identity – an assumption to perform the following univariate tests.

Moreover correction factors (ϵ) are shown which are used in 3 of the following 4 univariate tests.

If an ϵ is near to 1 the respective test would be overcorrecting (don't use it).

If the above test is not significant, sphericity is assumed.

Remark:

"proving" assumptions leads to known problems (see basic)



Hypertension: Within Subject Effect (time)

Univariate Test Results

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
TIME	Sphericity Assumed	58328,114	3	19442,705	3522,779	,000	,909
	Greenhouse-Geisser	58328,114	1,447	40322,646	3522,779	,000	,909
	Huynh-Feldt	58328,114	1,471	39640,824	3522,779	,000	,909
	Lower-bound	58328,114	1,000	58328,114	3522,779	,000	,909
TIME * GENDER	Sphericity Assumed	1922,972	3	640,991	116,140	,000	,247
	Greenhouse-Geisser	1922,972	1,447	1329,365	116,140	,000	,247
	Huynh-Feldt	1922,972	1,471	1306,886	116,140	,000	,247
	Lower-bound	1922,972	1,000	1922,972	116,140	,000	,247
TIME * THERAPY	Sphericity Assumed	7187,144	6	1197,857	217,037	,000	,551
	Greenhouse-Geisser	7187,144	2,893	2484,262	217,037	,000	,551
	Huynh-Feldt	7187,144	2,943	2442,256	217,037	,000	,551
	Lower-bound	7187,144	2,000	3593,572	217,037	,000	,551
TIME * GENDER * THERAPY	Sphericity Assumed	11556,444	6	1926,074	348,981	,000	,663
	Greenhouse-Geisser	11556,444	2,893	3994,527	348,981	,000	,663
	Huynh-Feldt	11556,444	2,943	3926,983	348,981	,000	,663
	Lower-bound	11556,444	2,000	5778,222	348,981	,000	,663
Error(TIME)	Sphericity Assumed	5861,325	1062	5,519			
	Greenhouse-Geisser	5861,325	512,073	11,446			
	Huynh-Feldt	5861,325	520,881	11,253			
	Lower-bound	5861,325	354,000	16,557			

This is a very easy situation as every test and even the uncorrected "Sphericity assumed" form shows the same significant result for the within effect in all groups.

The same result that we found with the multivariate tests.



Hypertension: Other Effects

Univariate Corrected Test Results

Tests of Between-Subjects Effects

Measure: MEASURE_1

Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	28179777,3	1	28179777,34	401381,4	,000	,999
GENDER	2006,944	1	2006,944	28,586	,000	,075
THERAPY	5217,372	2	2608,686	37,157	,000	,174
GENDER * THERAPY	13057,072	2	6528,536	92,990	,000	,344
Error	24853,275	354	70,207			

As we already found that all variables here are involved in significant interactions with time.

It would make no sense to interpret results here.

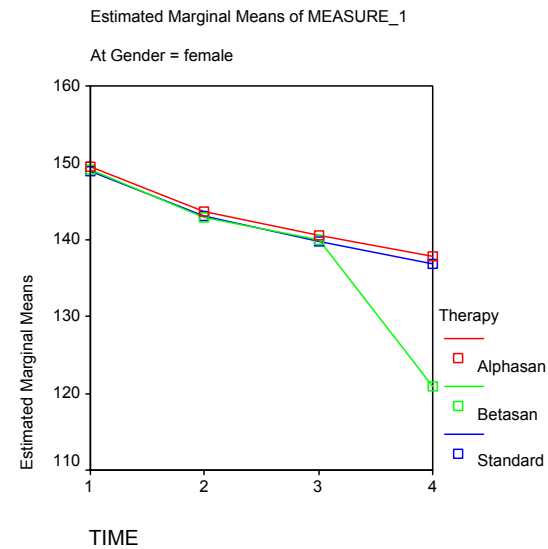
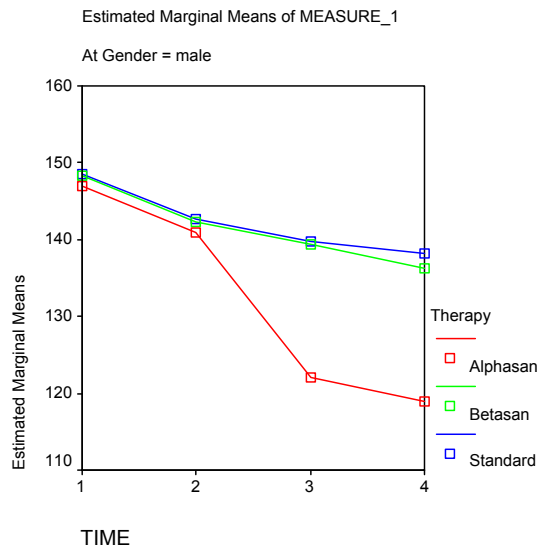
Remark:

As the former test on sphericity (**Mauchly's-Test**) is highly significant, univariate tests here should also be read with caution (see SAS).

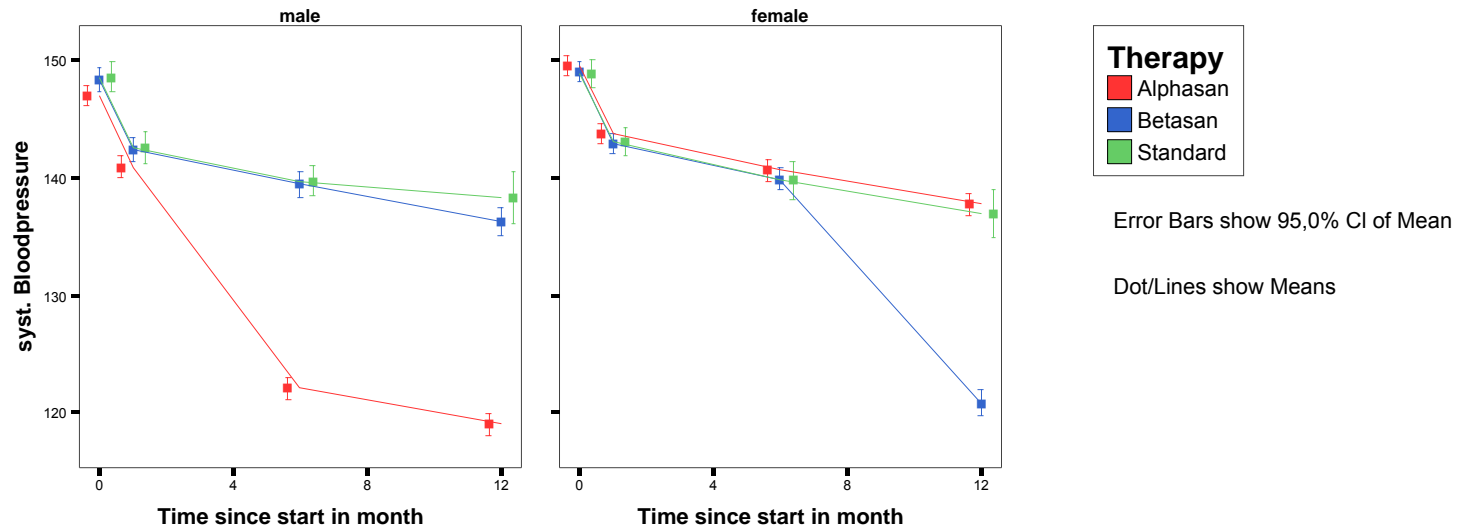


Hypertension: Marginal Mean Plots

As all interactions are significant we concentrate immediately on the analysis of crossed factors with Bonferroni-tests, confidence intervals and plots



Hypertension: Mean Confidence Plots and Résumé



A nice result.

It shows that Alphasan and Betasan are affecting male and female differently.

- For Betasan no difference to standard treatment is found in male patients (the same is true for Alphasan in female).
- Moreover both drugs show different time profiles in male and female:
Alphasan is smoothly lowering blood pressure after 1 month in male
while Betasan dramatically lowering the blood pressure in female after 6 months of treatment.

