

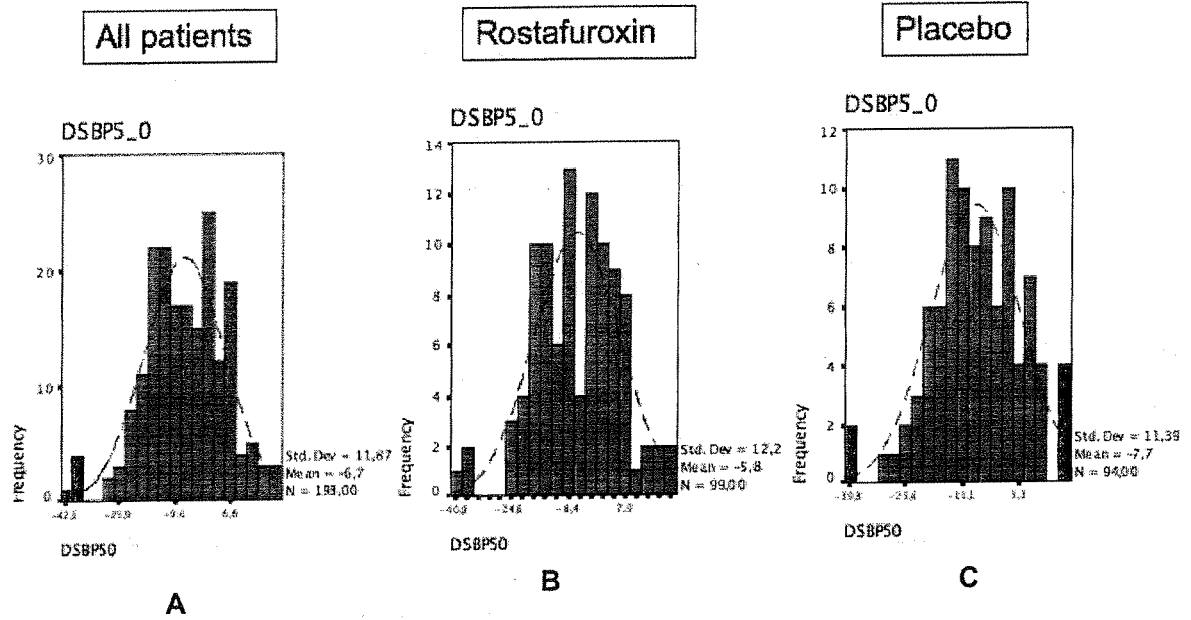


FIG. 1

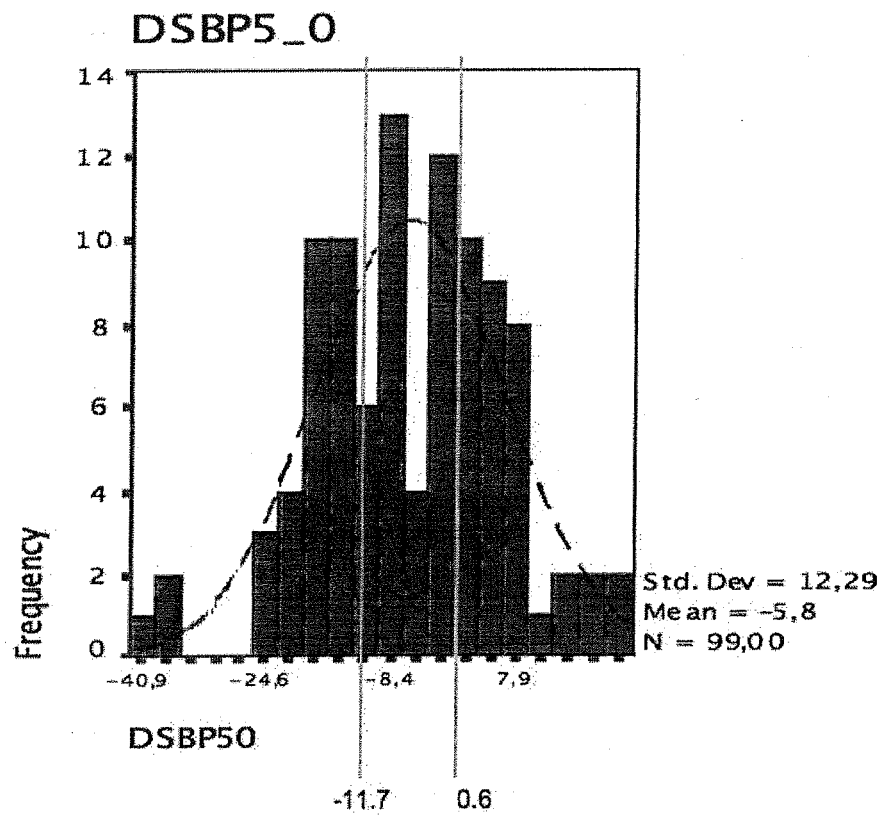


FIG. 2

3/10

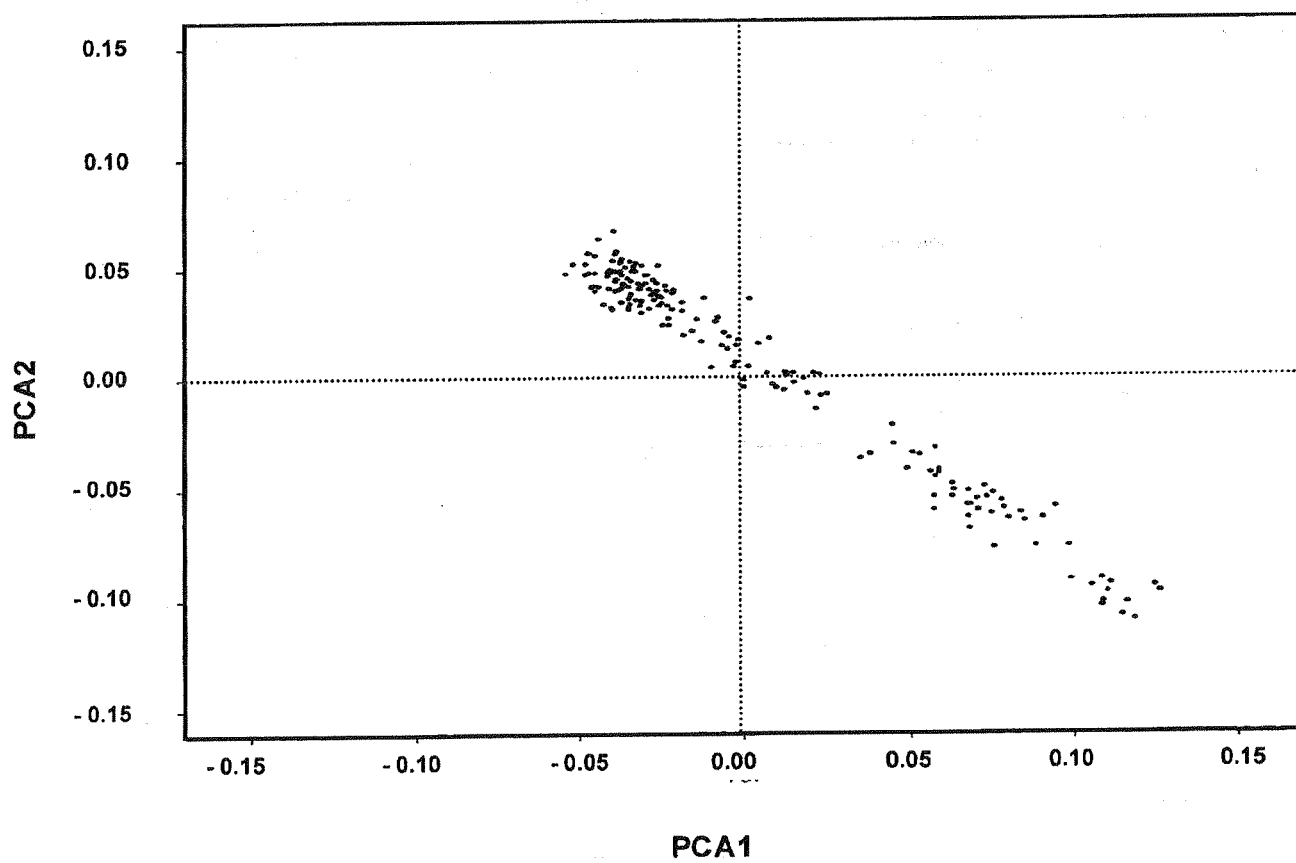


FIG. 3

4/10

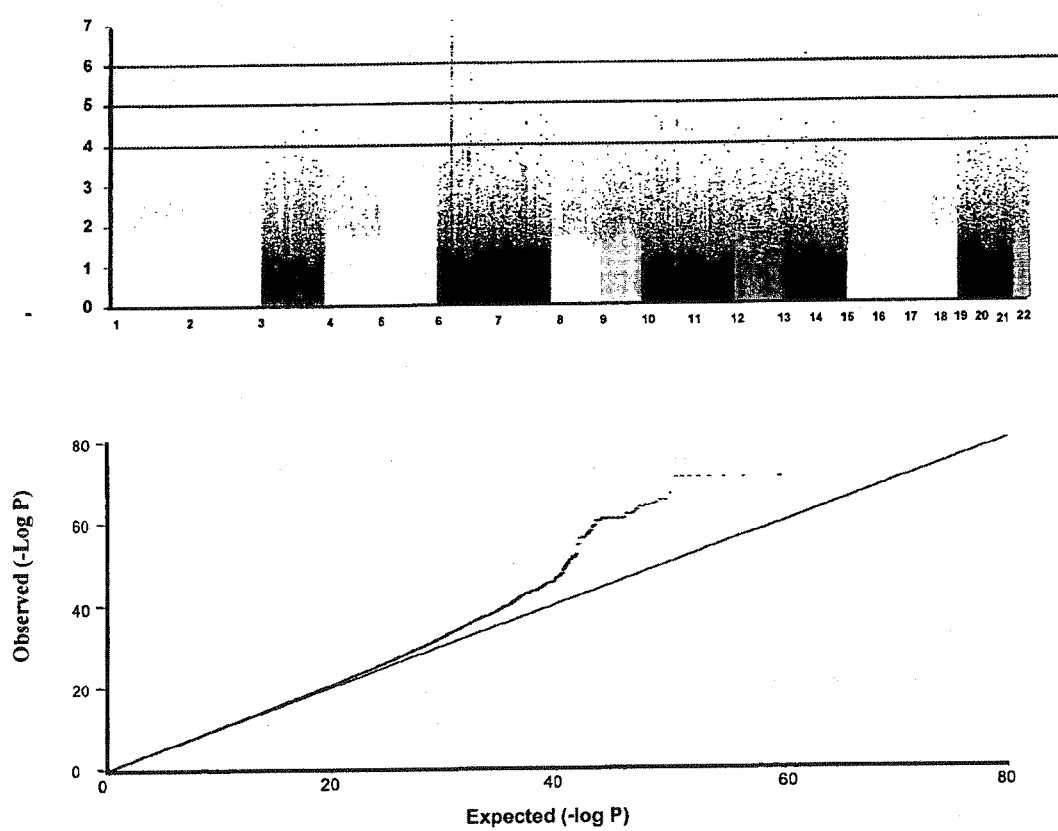


FIG. 4

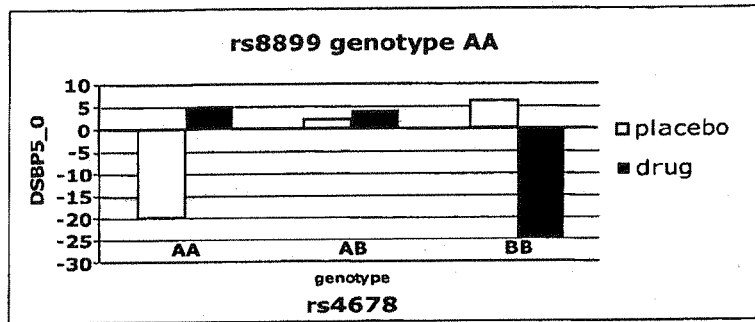
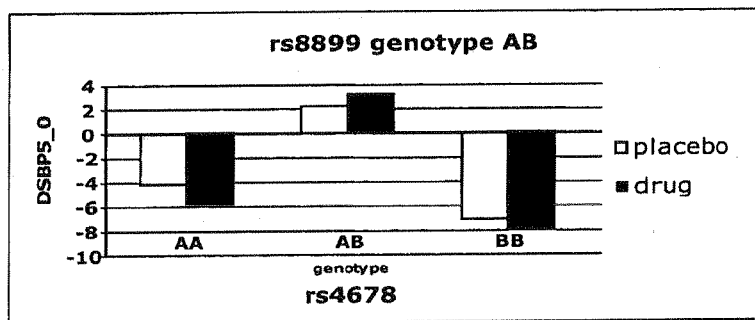
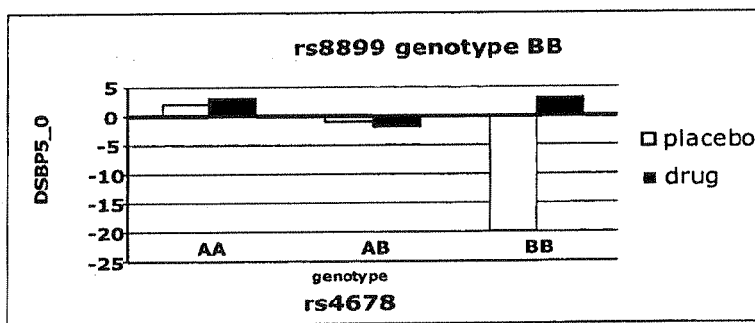


FIG. 5

1) ANOVA analysis of rs2461911 for placebo group:

Summary of DSBP50				
rs2461911	Mean	Std. Dev.	Freq.	
1 2.2166667	10.168268		6	
2 -6.7055556	11.987897		36	
3 -9.4923076	10.596815		52	
Total -7.6776596	11.390603		94	

Analysis of Variance				
Source	SS	df	MS	F Prob >
Between groups	792.638933	2	396.319467	
3.20 0.0454				
Within groups	11273.7243	91	123.88708	
Total	12066.3632	93	129.745841	

2) ANOVA analysis of rs2461911 for therapy group:

Summary of DSBP50				
rs2461911	Mean	Std. Dev.	Freq.	
1 -20.6	12.67024		5	
2 -7.9238095	12.361344		42	
3 -2.7211539	10.96131		52	
Total -5.8313131	12.294097		99	

Source	SS	df	MS	F Prob >
Between groups	1777.46998	2	888.734988	
6.55 0.0022				
Within groups	13034.7227	96	135.778362	
Total	14812.1927	98	151.144824	

FIG. 6

7/10

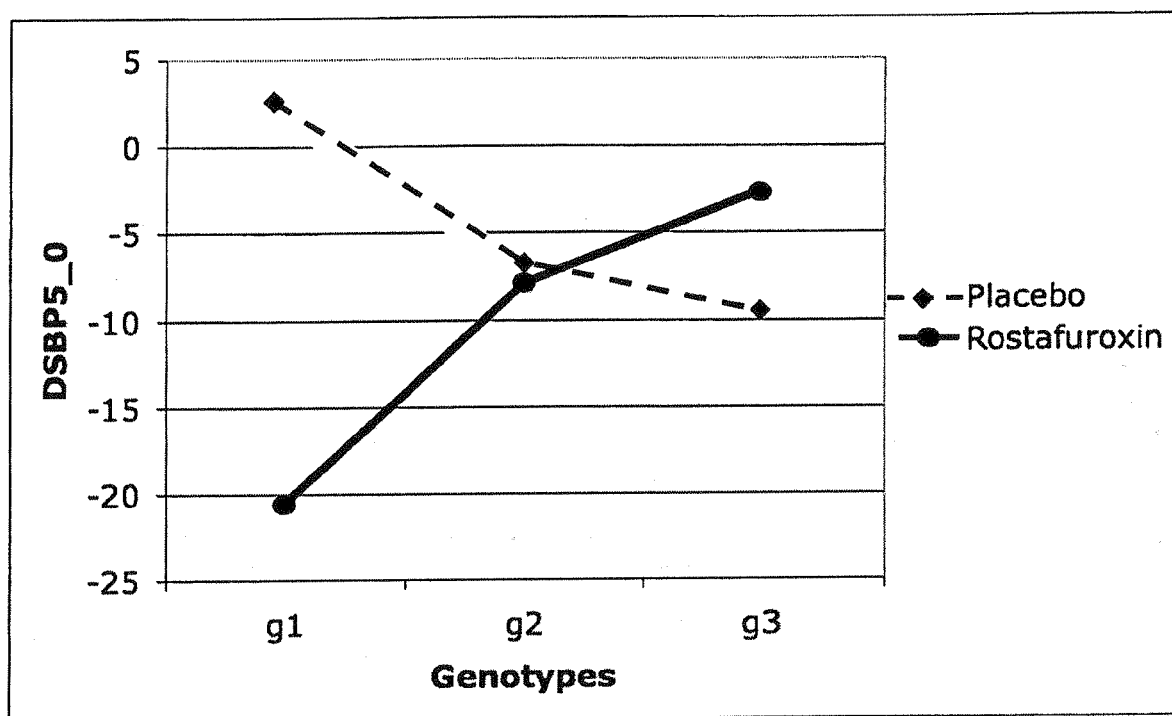


FIG. 7

	Profile 4	Profile 8	Profile 9
Response to treatments	rs16893522 rs5013093 rs2345088 rs2461911 rs16877182 rs12513375	Profile 4 MDR2- HSD18 LSS2- MDR2 LSS2- ADD1 HSD19- rs430948 MDR2- rs213112 ADD2- rs105029 LSS2- WNK	Profile 4 MDR2- HSD18 LSS2- MDR2 HSD19- rs473903 HSD19- rs430948 ADD2- rs105029 LSS2- WNK
pvalue	0.000	0.000	0.000
OddsRatio	14.64	32.62	69.75
sensitivity (se) %	54.5	82	82
PPV %	78.3	93	96
Correctly %	79.8	83	85
# true R	18/33	29/33	31/33
# true NR	61/66	54/66	54/66
DSBP5-0 Therapy (mmHg) mean $\pm$ SE (n)			
Treated with low doses	-18.74 $\pm$ 1.8	-15.2 $\pm$ 1.5	-15.2 $\pm$ 1.5
Treated with high doses	-23.12 $\pm$ 3.2 (10)	-17.9 $\pm$ 2.05 (22)	-18.0 $\pm$ 2.0 (22)
	-15.2 $\pm$ 3.0 (13)	-12.6 $\pm$ 2.4 (19)	-12.3 $\pm$ 2.2 (21)
DSBP5-0 Placebo (mmHg) mean	-1.14	-2.57	-2.64
Losartan	-11.37	-11.63	-11.43
HCTZ	-12.34	-11.36	-11.95
Patients with profile treated / placebo	23 / 28	41 / 43	43 / 44
Patients with profile	51	84	87
Patients with profile (%)	26%	42.8%	44.4%
(196 patients)			

FIG. 8

N	Gene Symbol	Chr	Gene name
1	ACE1	17	angiotensin I converting enzyme (peptidyl-dipeptidase A) 1
2	ACE2	X	angiotensin I converting enzyme (peptidyl-dipeptidase A) 2
3	ACTA1	1	actin, alpha 1, skeletal muscle
4	ACTA2	10	actin, alpha 2, smooth muscle, aorta
5	ACTN1	14	actinin, alpha 1
6	ADRA1A	8	adrenergic, alpha-1A-, receptor
7	ADRA2B	2	adrenergic, alpha-2B-, receptor
8	ADRB1	10	adrenergic, beta-1-, receptor
9	ADRB2	5	adrenergic, beta-2-, receptor
10	ADRB3	8	adrenergic, beta-3-, receptor
11	AGT	1	angiotensinogen
12	AGTR1	3	angiotensin II receptor, type 1
13	AGTR2	X	angiotensin II receptor, type 2
14	AQP2	12	aquaporin 2
15	ATP1A1	1	ATPase, Na+/K+ transporting, alpha 1 polypeptide
16	ATP1A2	1	ATPase, Na+/K+ transporting, alpha 2 (+) polypeptide
17	ATP1A3	19	ATPase, Na+/K+ transporting, alpha 3 (+) polypeptide
18	ATP1A4	1	ATPase, Na+/K+ transporting, alpha 4 (+) polypeptide
19	ATP1B1	1	ATPase, Na+/K+ transporting, beta 1 polypeptide
20	ATP1B2	17	ATPase, Na+/K+ transporting, beta 2 polypeptide
21	ATP1B3	3	ATPase, Na+/K+ transporting, beta 3 polypeptide
22	ATP1B4	X	ATPase, Na+/K+ transporting, beta 4 polypeptide
23	BSND	1	Bartter syndrome, infantile, with sensorineural deafness
24	CLCNKA	1	chloride channel Ka
25	CLCNKB	1	chloride channel Kb
26	CLTA	12	clathrin, light chain (Lca)
27	CLTB	4	clathrin, light chain (Lcb)
28	CLTC	17	clathrin, heavy chain (Hc)
29	CLTCL1	22	clathrin, heavy polypeptide-like 1
30	CYP11B2	8	cytochrome P450, family 11, subfamily B, polypeptide 2
31	DRD1	5	dopamine receptor D1
32	DRD3	3	dopamine receptor D3
33	DRD4	11	dopamine receptor D4
34	DRD5	4	dopamine receptor D5
35	FXYP1	19	FXYP domain containing ion transport regulator 1
36	FXYP2	11	FXYP domain containing ion transport regulator 2
37	FXYP3	19	FXYP domain containing ion transport regulator 3
38	FXYP4	10	FXYP domain containing ion transport regulator 4
39	FXYP5	19	FXYP domain containing ion transport regulator 5
40	FXYP6	11	FXYP domain containing ion transport regulator 6
41	FXYP7	19	FXYP domain containing ion transport regulator 7
42	FXYP8	X	FXYP domain containing ion transport regulator 8
43	FYN	6	FYN oncogene related to SRC, FGR, YES [
44	GNB3	12	guanine nucleotide binding protein (G protein), beta polypeptide 3
45	KCNJ1	11	potassium inwardly-rectifying channel, subfamily J, member 1 (ROMK)
46	LYN	8	v-src-1 Yamaguchi sarcoma viral related oncogene homolog
47	NCL	2	nucleolin
48	NEDD4	15	neural precursor cell expressed, developmentally down-regulated 4
49	NEDD4L	18	neural precursor cell expressed, developmentally down-regulated 4-like
50	NKAIN1	1	Na+/K+ transporting ATPase interacting 1
51	NKAIN2	6	Na+/K+ transporting ATPase interacting 2
52	NKAIN3	8	Na+/K+ transporting ATPase interacting 3
53	NKAIN4	20	Na+/K+ transporting ATPase interacting 4
54	NOS3	7	nitric oxide synthase 3 (endothelial cell)
55	NPHS1	19	nephrosis 1, congenital, Finnish type (nephrin)
56	NPHS2	1	nephrosis 2, idiopathic, steroid-resistant (podocin)
57	PKD1	16	polycystic kidney disease 1 (autosomal dominant)
58	PKD2	4	polycystic kidney disease 2 (autosomal dominant)
59	REN	1	renin
60	RFX1	19	regulatory factor X, 1
61	RPH3A	12	rabphilin 3A homolog (mouse)
62	RPH3AL	17	rabphilin 3A-like (without C2 domains)
63	SCNN1A	12	sodium channel, nonvoltage-gated 1 alpha
64	SCNN1B	16	sodium channel, nonvoltage-gated 1, beta
65	SCNN1D	1	sodium channel, nonvoltage-gated 1, delta
66	SGK1	6	serum/glucocorticoid regulated kinase 1
67	SLC12A1	15	solute carrier family 12 (sodium/potassium/chloride transporters), member 1
68	SLC12A3	16	solute carrier family 12 (sodium/chloride transporters), member 3
69	SLC8A1	2	solute carrier family 8 (sodium/calcium exchanger), member 1
70	SYNPO	5	synaptopodin
71	SRC	20	v-src sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog (avian)
72	TJP1	15	tight junction protein 1 (zona occludens 1)
73	UMOD	16	uromodulin
74	WNK1	12	WNK lysine deficient protein kinase 1
75	WNK4	17	WNK lysine deficient protein kinase 4

FIG. 9

**Efficacy and safety data for new Antihypertensive Therapies:
comparison between Traditional and Innovative Pharmacogenomic Approaches**

Parameter	Traditional	Pharmacogenomic (Rostafuroxin data)
<u>Antihypertensive Efficacy</u> (Δ Systolic BP mmHg, minus placebo)	-6 / -12	-14 / -23
<u>Superiority among Drug Classes</u> (Δ SBP, mmHg, in never treated patients)	0 / -3	-5 / -11
<u>Reduction of CV complications</u>	20-30%	not yet assessed, but expected to be superior *
<u>Safety ratio</u> (in preclinical models)	1:20 – 1:40	> 1: 10.000

n.b. The comparison between the traditional and new approach, considers similar treatment duration and basal BP levels of the patients.

* the improved prevention of CV complications is expected due to the better BP control and the selective targeting of the genetic alterations (gene profile) responsible for the CV complications.

FIG. 10