Tolerance of Telmisartan and Ramipril among Asians & additional PPAR effects

고려대학교 구로병원

심혈관 센터

서 홍 석

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Telmisartan, Ramipril, or Both in Patients at High Risk for Vascular Events

The ONTARGET Investigators*

Primary Outcome

	Overall	Asian	Nonasian	p-value
Telmisartan*	16.7%	14.6%	17.0%	0.775
Ramipril*	16.5%	16.1%	16.5%	0.082
Relative Risk* (95% CI)	1.01 (0.94-1.09)	0.92 (0.74-1.13)	1.03 (0.95-1.11)	0.305
p-value	0.004	0.04	0.02	–

* No significant difference between asians and non-asians

Racial Differences in CVD

- Gene Polymorphysm – ACE, Bleeding tendency etc.
- Risk Factors -

  Blood lipid profile –LDL dominant, TG dominant

  Salt intake and Hypertension

  Obesity and Diabetic susceptibility

  Diet
- CVD difference -

  Stroke-prone vs CHD-prone
- Others –Drug side effect, Body weight and height, etc.

Baseline Characteristics of Asians and Non-Asians in the ONTARGET and TRANSCEND studies.

	ONTARGET		TRANSCEND	
	ASIANS	NON-ASIANS	ASIANS	NON-ASIANS
	(n = 3521)	(n = 22,092*)	(n = 1261)	(n = 4665)
Mean age (years)	65.48	66.58	65.64	67.2
Male Sex (%)	73.7	73.3	59.7	56.3
Hypertension (%)	69.1	68.7	73.4	77.2
Diabetes (%)	43.1	36.6	41.7	34.1
Stroke or TIA (%)	30.3	19.3	34.2	18.7
Coronary disease (%)	71.1	75.1	70.1	75.8
Current Smokers (%)	12.3	12.6	10.6	9.6
Mean Systolic BP (mmHg)	141	142	140	141
Mean BMI (KG/m^2)	25.5	28.51	25.9	28.73
Mean cholesterol (mmol/Li)	4.97	4.94	4.99	5.11
Mean HDL (mmol/Li)	1.25	1.26	1.27	1.28
Mean LDL (mmol/Li)	2.95	2.92	2.98	3.04
Mean triglycerides (mmol/Li)	1.73	1.73	1.77	1.78
Fasting glucose (mmol/Li)	6.73	6.67	6.55	6.49
Prior coronary bypass (%)	11.0	23.9	10.3	21.2
Prior PTCA (%)	35.1	28.1	32.4	24.5
Statin use (%)	49.5	63.5	48.4	57.1
Beta-Blocker use (%)	52.2	57.7	52.0	60.0
Aspirin use (%)	77.6	75.4	73.5	75.0
Thienopyridine use (%)	9.1	11.3	10.7	10.7
Diuretic use (%)	18.1	29.5	22.5	35.8
Calcium blocker use (%)	43.9	31.3	50.0	37.5

Problem in the Asia-Pacific

1. Can patients reach the target doses used?
2. Can we tolerate the doses at which the drugs were given?

ONTARGET
Asian
sub-data

% Achieving Full Dose at Last Visit

	Overall	Asians	Nonasians
Single Drug			
Ramipril	74.8%	77.9%	74.3%
Telmisartan	79.8%	87.6%*	78.6%*
Combination			
Ramipril	66.9%	71.5%*	66.2%*
Telmisartan	75.6%	82.9%*	74.4%*

* $P < 0.001$

Percent of Patients Achieving Full Dose Ramipril, Telmisartan or placebo at the end of the ONTARGET and TRANSCEND studies.

	Overall	Asians	Non-Asians	p-value[†]
ONTARGET				
Ramipril	5730 (74.82%)	826 (77.92%)	4903 (74.32%)	0.012
Telmisartan	6103 (79.82%)	922 (87.56%)	5180 (78.60%)	0.0001
RR (95% CI)[*]	1.08(1.05,1.09)	1.12(1.08,1.17)	1.06(1.04,1.08)	0.0003[§]
p-value[¶]	<0.0001	<0.0001	<0.0001	-
TRANSCEND				
Placebo	2088 (79.09%)	501 (86.68%)	1587 (76.96%)	<0.0001
Telmisartan	2086 (79.44%)	500 (86.36%)	1586 (77.48%)	<0.0001
RR (95% CI)[**]	1.00(0.98,1.03)	1.00(0.95,1.04)	1.01(0.97,1.04)	0.762[§]
p-value[δ]	0.757	0.872	0.694	-

Permanent Withdrawals (Ramipril vs Telmisartan)

	Overall		Asians		Non-Asians	
	R	T	R	T	R	T
Discontinued	24.7%	23.4%	19.9%*	14.4%ϕ	25.5%*	24.8%ϕ
Hypotension	1.5%	2.1%	1.0%	0.8%ϕ	1.6%	2.3%ϕ
Syncope	0.2%	0.2%	0.1%	0.3%	0.2%	0.2%
Cough	4.1%	1.0%	5.9%*	1.4%	3.8%*	1.0%
Diarrhea	0.1%	0.2%	--	0.2%	0.2%	0.2%
Angioedema	0.3%	0.1%	0.2%	--	0.3%	0.1%
Renal impairment	0.6%	0.6%	0.3%	0.4%	0.6%	0.6%

* $p < 0.0001$ (asians vs non-asians)

ϕ $p < 0.0001$ (asians vs non-asians)

Overall Discontinuations in Percent, in ONTARGET and TRANSCEND.

	Overall	Asians	Non-Asians	p-value[†]
ONTARGET Study				
Ramipril	2121 (24.73%)	235 (19.88%)	1885 (25.50%)	<0.0001
Telmisartan	2000 (23.41%)	169 (14.42%)	1829 (24.83%)	<0.0001
RR (95% CI)[*]	0.95 (0.90,1.00)	0.73 (0.61,0.87)	0.97 (0.92,1.03)	0.003[§]
p-value[¶]	0.044	0.0004	0.346	-
TRANSCEND Study				
Placebo	705 (23.72%)	82 (13.14%)	623 (26.53%)	<0.0001
Telmisartan	639 (21.63%)	83 (13.03%)	556 (24.00%)	<0.0001
RR (95% CI)[**]	0.91 (0.83,1.00)	0.99(0.75,1.32)	0.9(0.82,1.00)	0.489[§]
p-value[δ]	0.055	0.953	0.046	-

Percent Permanent Discontinuations Because of Side effects in ONTARGET and TRANSCEND.

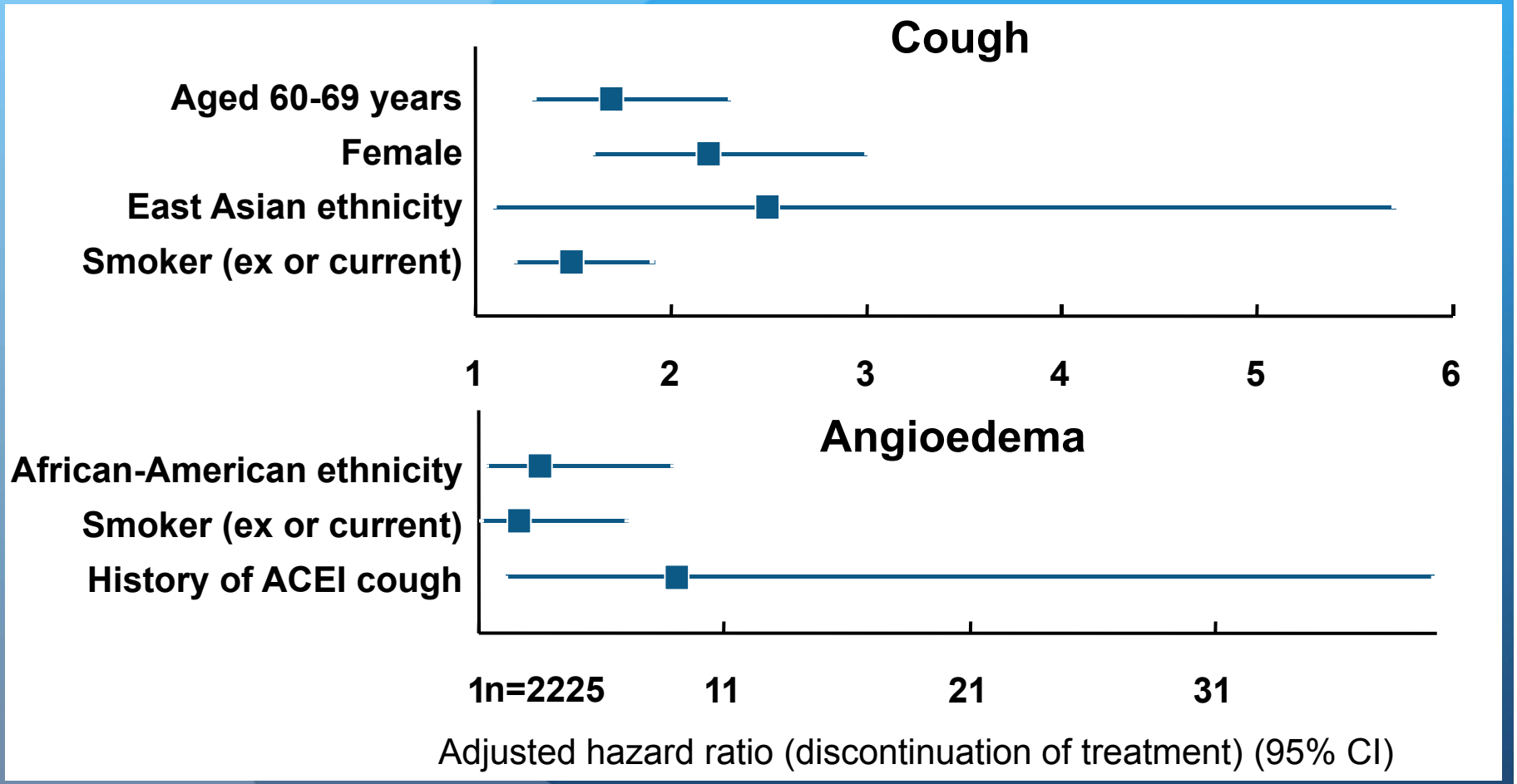
	Overall	Asians	Non-Asians	p-value[†]
ONTARGET Study				
Ramipril	1005(11.72%)	135(11.42%)	869 (11.76%)	0.740
Telmisartan	835(9.78%)	77 (6.57%)	757 (10.28%)	0.0001
RR (95% CI)[*]	0.83(0.76,0.91)	0.58(0.44,0.75)	0.87 (0.80,0.96)	0.004[§]
p-value[¶]	<0.0001	<0.0001	0.004	-
TRANSCEND Study				
Placebo	163 (5.49%)	18 (2.89%)	145 (6.18%)	0.001
Telmisartan	214 (7.24%)	22(3.45%)	192 (8.29%)	<0.0001
RR (95% CI)[**]	1.32 (1.08,1.61)	1.2(0.65,2.21)	1.34(1.09,1.65)	0.702[§]
p-value[δ]	0.006	0.564	0.005	-

Side effects of ACE inhibitor therapy limit tolerability and increases non-adherence

- Cough affects up to 35% of patients treated with ACE inhibitors[1]
  - Treatment should be discontinued irrespective of the temporal relationship between onset of cough and treatment initiation
- Angio-edema affects 0.1–0.7% of patients receiving ACE inhibitors[2,3]
  - Immediate discontinuation of treatment is essential

1. Dicpinigaitis PV. Chest 2006;129(Suppl 1):169S-173S
2.Miller DR, et al. Hypertension 2008;51:1624-1630
3. Weber MA, & Messerli FH. Hypertension 2008;51:1465-1367.

Who is at greatest risk of ACEI adverse events?



Morimoto et al. J Eval Clin Practice 2004;10:499-509

Who is at greatest risk of ACEI adverse events?

N=356	Cough=144	Non-cough=212	p value
Age	55.9±11.7	57.3±11.9	NS
Sex (M : F)	43 : 101	116 : 95	<0.0001
DM	21/140 (15.0%)	31/203 (15.3%)	NS
Smoking (yes : no)	18/124 (14.5%)	46/212 (21.7%)	0.031
ACEI MED			
CTP : ENL : PRDP	19 : 61 : 64	37 : 99 : 72	NS
β : CCB : diuretics	40 : 52 : 32	64 : 88 : 42	NS
LVH (yes : no)	42 : 37 (47.2%)	68 : 77 (46.9%)	NS
f/u duration	25±16 m	26±12 m	NS
EF (baseline, %)	57.1±11.9	51.8±15.9	NS
PACE			
II : ID : DD	56 : 44 : 31	74 : 76 : 37	NS

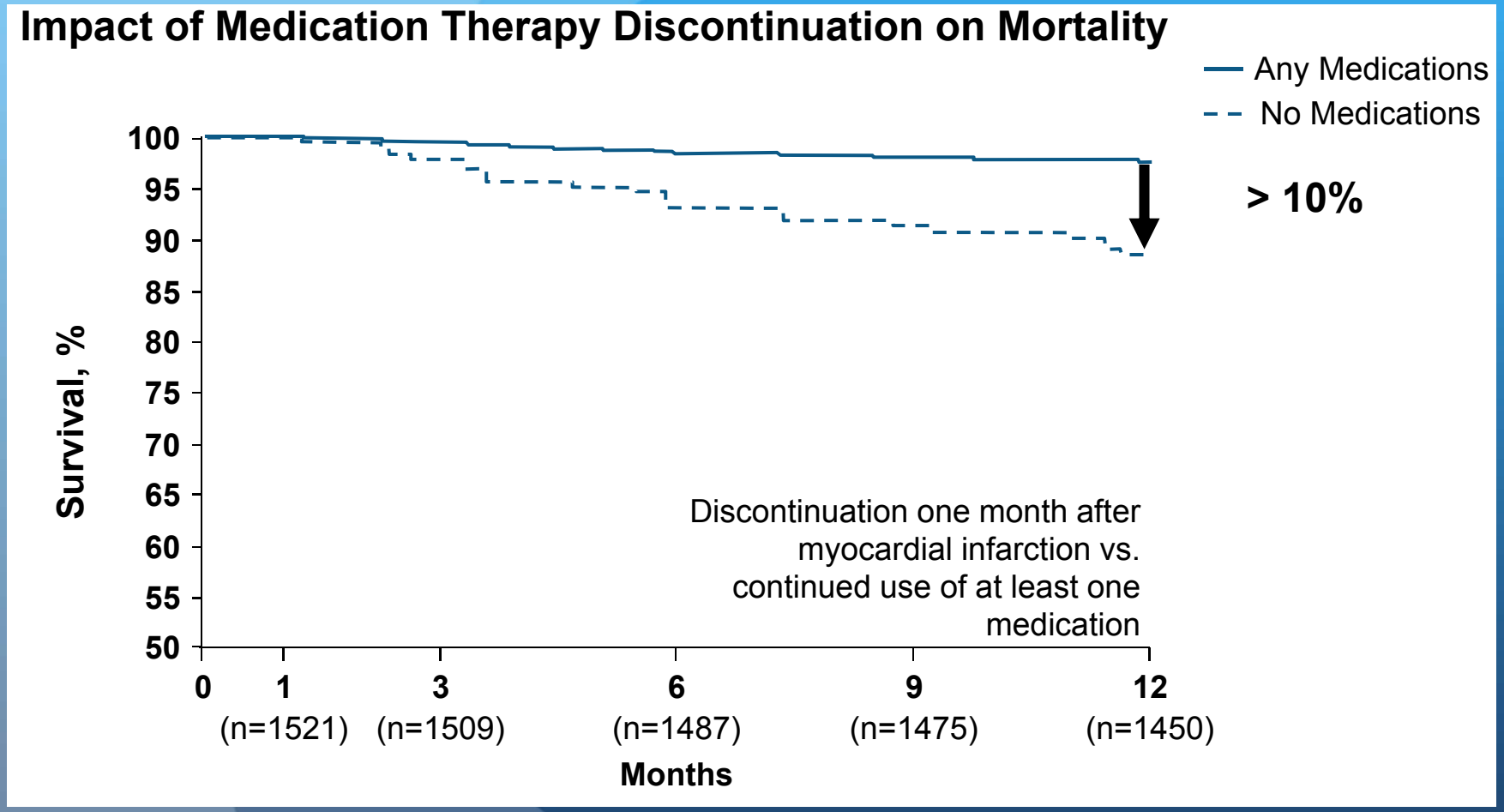
Variable	Significance	OR (95% CI)
Age	0.26	1.01 (0.99 - 1.02)
Sex (Female)	<0.001	2.89 (1.83 - 4.50)
DM	0.94	1.02 (0.55 - 1.86)
Non-smokier	0.06	1.90 (0.97 - 3.45)
LVH (yes)	0.97	0.98 (0.58 - 1.68)
ACE medication	0.15	1.44 (0.90 - 2.29)
ACE polymorphism	0.41	0.79 (0.46 - 1.37)

나상훈 외. Korean Circulation J 2000;30(12):1540-1545

Percent Discontinuations Because of Cough in the ONTARGET Study.

	Overall	Asians	Non-Asians	p-value[†]
Ramipril	360 (4.2%)	72 (6.1%)	288(3.9%)	<0.001
Telmisartan	93(1.1%)	17(1.45%)	76 (1.03%)	0.200
RR (95% CI)[*]	0.26 (0.21,0.33)	0.24 (0.14,0.4)	0.26 (0.21,0.34)	0.679[§]
p-value[δ]	<0.0001	<0.0001	<0.0001	

Patients who discontinue medications are at increased mortality risk



Ho et al. Arch Intern Med 166 (2006): 1842-1847

Permanent Withdrawals on R & T

	Asians		Non-Asians	
	Ramip	Telmi	Ramip	Telmi
Discontinuations	19.9%	14.4%	25.5%	24.8%
Hypotension	1.0%	0.8%	1.6%	2.3%
Syncope	0.1%	0.3%	0.2%	0.2%
Cough	5.9%	1.4%	3.8%	1.0%
Diarrhea	--	0.2%	0.2%	0.2%
Angioedema	0.2%	--	0.3%	0.1%
Renal impairment	0.3%	0.4%	0.6%	0.6%

Reasons for Permanent Withdrawals on Combination

	Asians	Non-Asians
Discontinuations	20.9%	31.7%
Hypotension	1.9%	4.7%
Syncope	0.5%	0.3%
Cough	5.9%	4.3%
Diarrhea	0.1%	0.5%
Angioedema	--	0.2%
Renal impairment	0.3%	1.0%

Primary Outcomes on R & T

	Asians		Non-Asians	
	Ramip	Telmi	Ramip	Telmi
MI	4.5%	3.2%	4.9%	5.5%
Stroke	5.6%	6.2%	4.6%	4.0%
CHF hosp.	3.4%	3.7%	4.2%	4.8%
CV Death	6.5%	5.7%	7.1%	7.2%
Non-CV Death	4.7%	5.1%	4.8%	4.5%
All Deaths	11.2%	10.8%	11.9%	11.7%
Primary Outcome	16.1%	14.6%	16.5%	17.0%

Secondary Outcomes on R & T

	Asians		Non-Asians	
	Ramip	Telmi	Ramip	Telmi
Revascularization	11.8%	10.1%	15.3%	15.9%
Angina w hosp.	10.6%	9.7%	10.8%	11.4%
New/worse angina	5.0%	4.2%	6.9%	6.6%
New DM	9.2%	8.8%	6.4%	7.4%
Any CHF	4.9%	5.0%	6.2%	6.5%

Secondary Outcomes on Combination

	Asians	Non-Asians
Revascularization	11.0%	16.0%
Angina w hosp.	10.4%	11.3%
New/worse angina	3.4%	6.8%
New DM	7.8%	5.9%
Any CHF	4.3%	5.8%

Renal Outcomes on R & T

	Asians		Non-Asians	
	Ramip	Telmi	Ramip	Telmi
Renal impairment*	10.6%	10.4%	10.1%	10.6%
Need for Dialysis*	0.5%	0.4%	0.6%	0.6%
Crea > 2x rise*	2.6%	2.4%	1.7%	1.9%
K > 5.5*	3.4%	3.4%	3.3%	3.4%

* No significant difference between asians and non-asians

Renal Outcomes on Combination

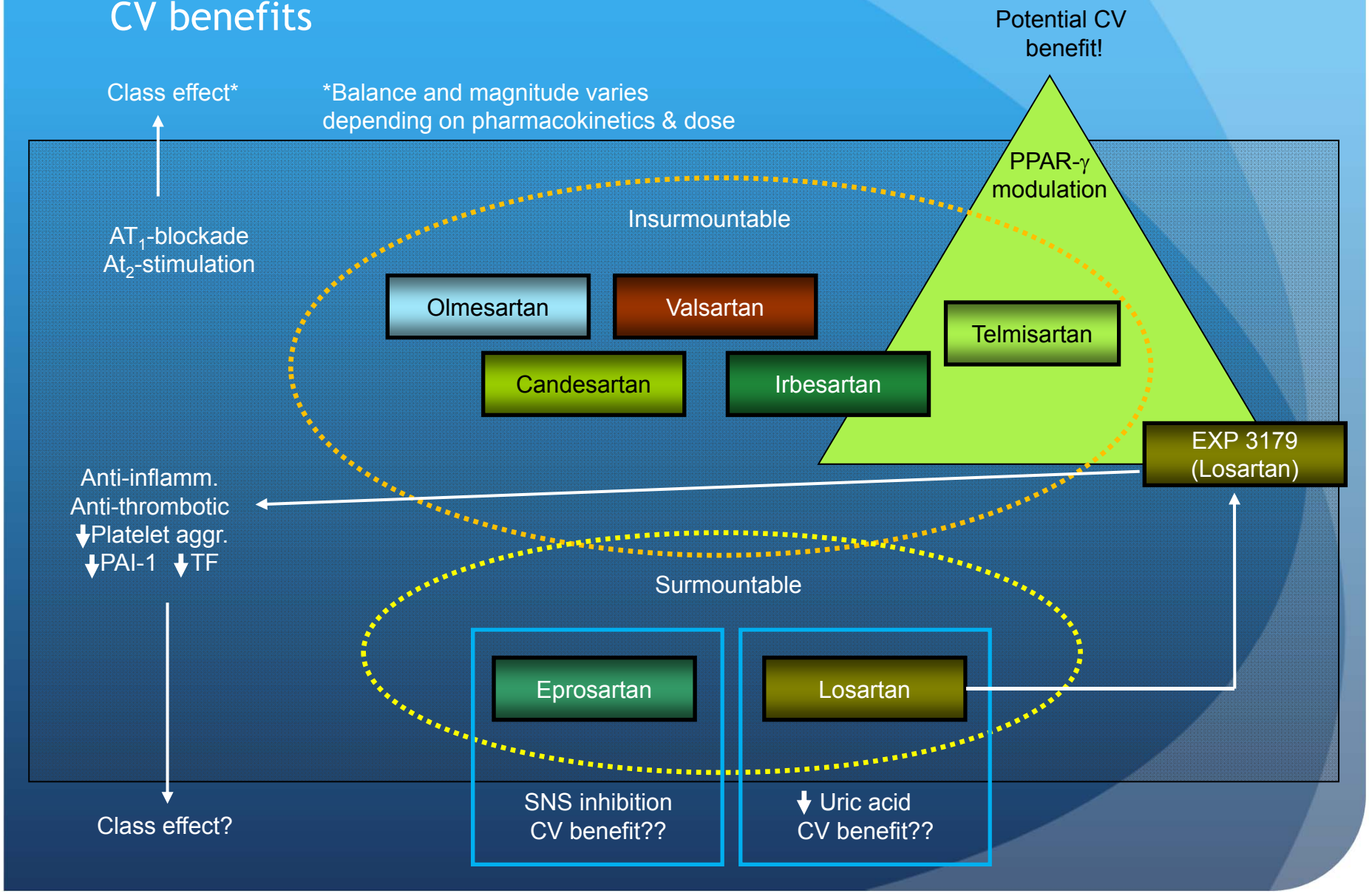
	Asians	Non-Asians
Renal impairment	12.9%	13.6%
Need for Dialysis	1.0%	0.7%
Crea > 2x rise	2.9%	2.0%
K > 5.5	5.7%	5.6%

Problem in the Asia-Pacific

1. Can patients reach the target doses used?
2. Can we tolerate the doses at which the drugs were given?

ARB differences

CV benefits



Pharmacological profile of telmisartan

- Highly selective, insurmountable AT_1 receptor blocker with strong binding affinity
- Long terminal plasma elimination half-life (~24 hours)
- Highly lipophilic, easily distributed into tissues (volume of distribution = ~500 L)
- Metabolised in liver to inactive acylglucuronide
- Excreted via bile in faeces; <1% urinary excretion
- Not a pro-drug; no active metabolites
- Partial PPARγ activation

Maillard M.P., *et al*. J Pharmacol Exp Ther 2002;302:1089–1095
Kakuta H., *et al*. Int J Clin Pharmacol Res 2005;25:41–46;
Burnier M .& Maillard M., Blood Press 2001;10:6–11;
Stangier J., *et al*. J Int Med Res 2000;28:149–167;
Stangier J., *et al*. *J Clin Pharmacol* 2000;40:1312–1322

Effect of telmisartan on Fat metabolism

- PPARγ activation : insulin sensitivity↑
- PPARδ activation :

  FFA oxidation↑ – lipolysis↑

  HSL activation, lipoprotein lipase activation

  UCP activation – energy uncoupleing – promotion of caloric expenditure

  Adiponectin↑, HDL↑

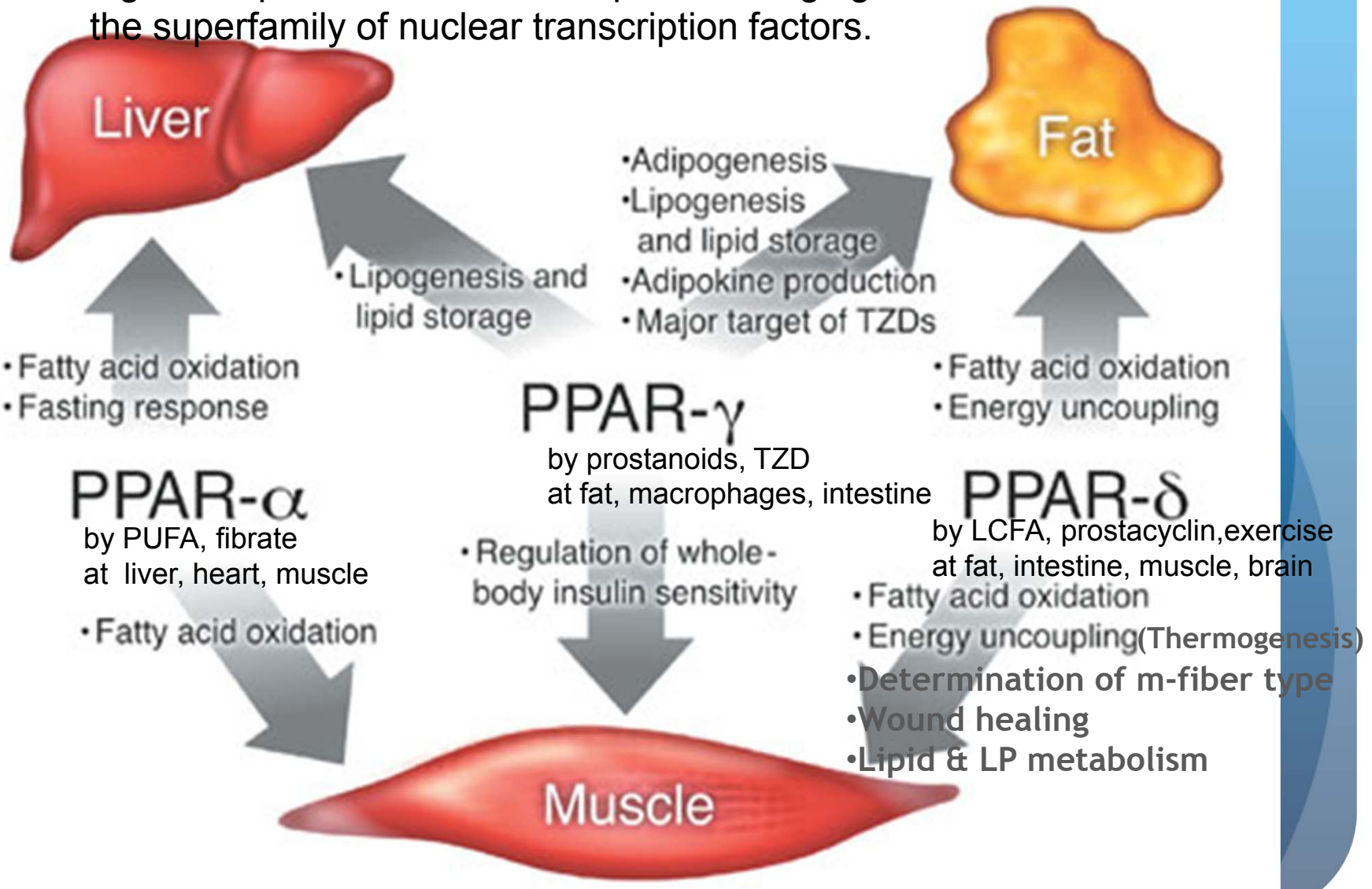
  Adipogenic activation- visceral adipocyte size ↓

  Reduction of body weight

He et al. Hypertension. 2010;55:869-879

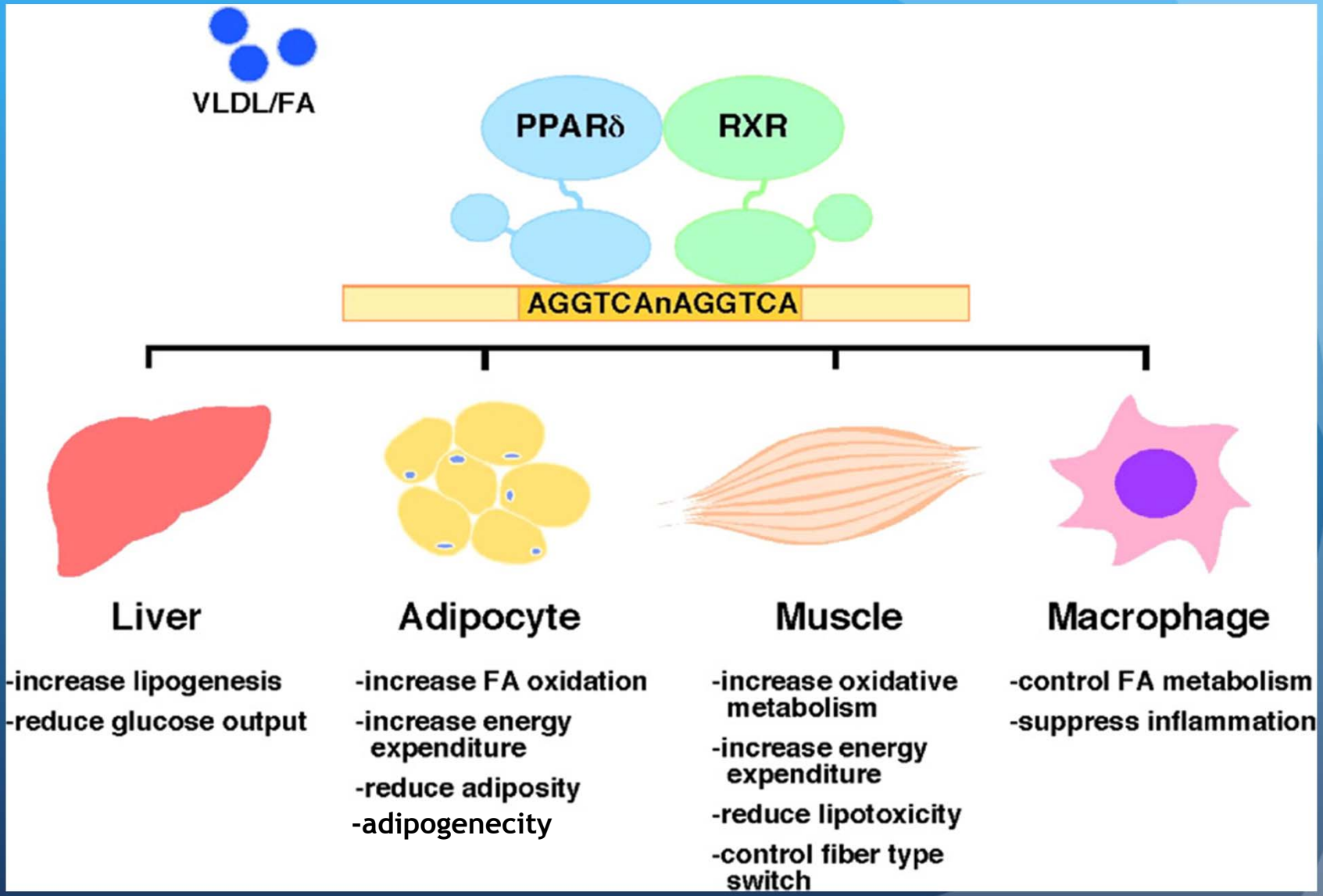
Peroxisome Proliferator-Activated Receptor Family

Ligand-dependent nuclear receptors belonging to the superfamily of nuclear transcription factors.



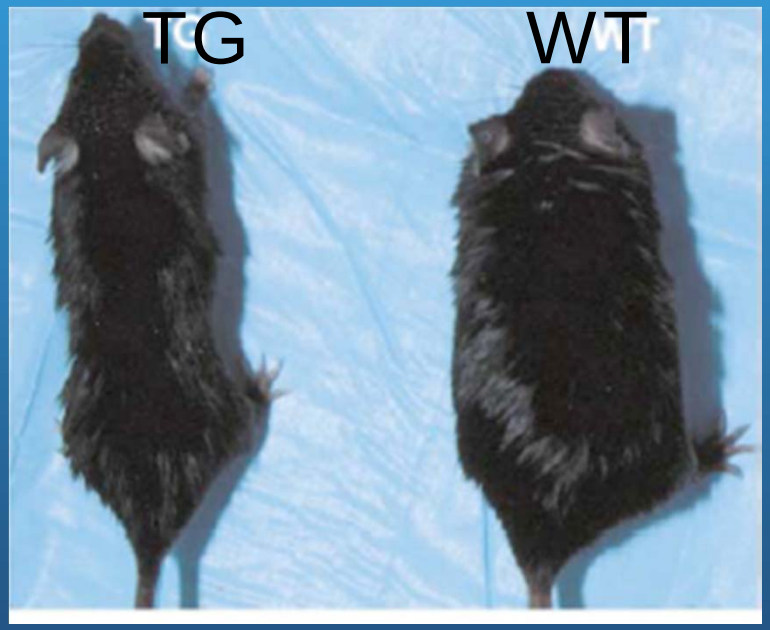
Lehrke M et al. Nature Medicine 2004;10:355-61

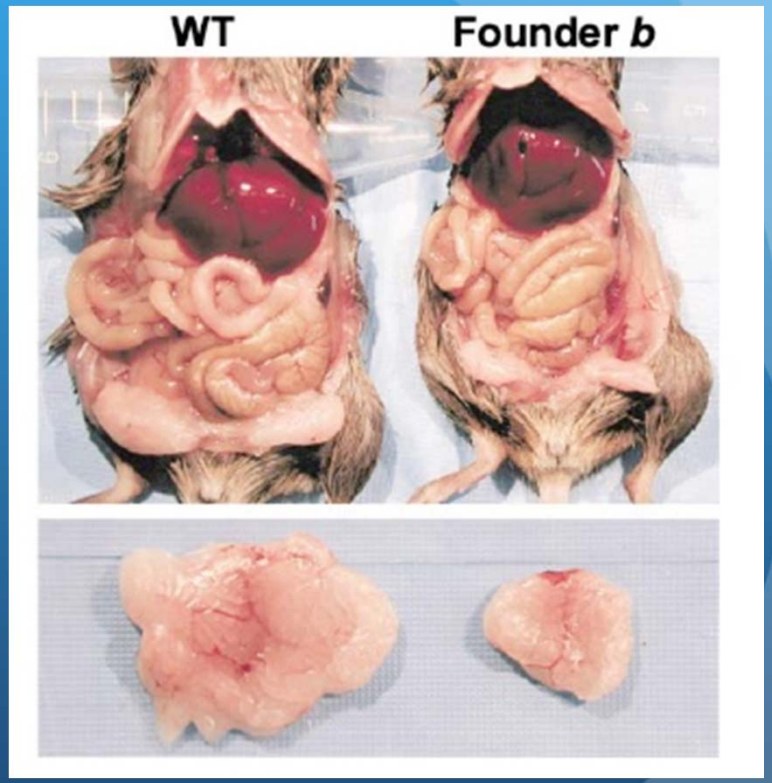
Transcriptional regulation of metabolic homeostasis by PPARδ



Reilly et al. FEBS Letters 582 (2008) 26–31

Overexpression of PPARβ/δ specifically in adipose tissue decreases fatty acid levels and protects against obesity

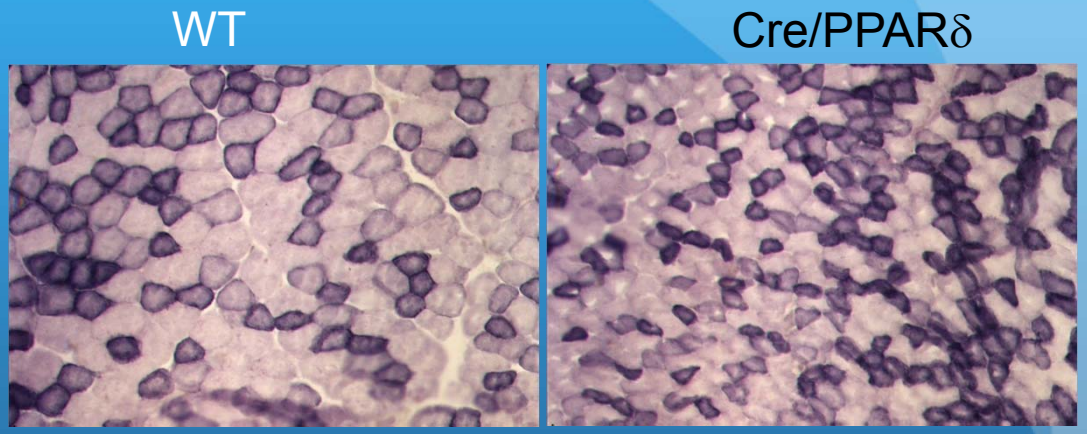




Wang YX, Lee CH, Tiep S, Yu RT, Ham J, Kang H, Evans RM.
Peroxisome-proliferator-activated receptor delta activates fat metabolism to prevent obesity.
Cell. 2003, 113: 159-170.

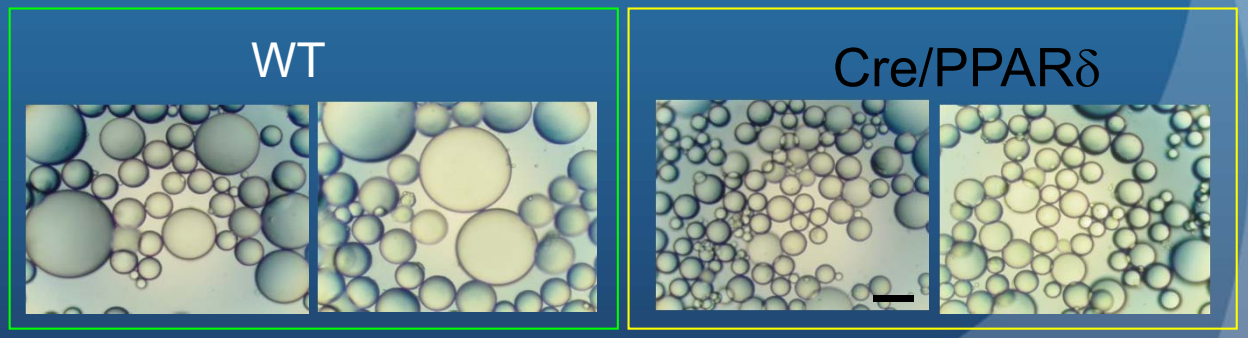
Overexpression of PPARβ/δ specifically in skeletal muscle (Cre/Lox system) increases fatty acid oxidation and promotes mitochondriogenesis

Increased number of oxidative fibers in transgenic mice



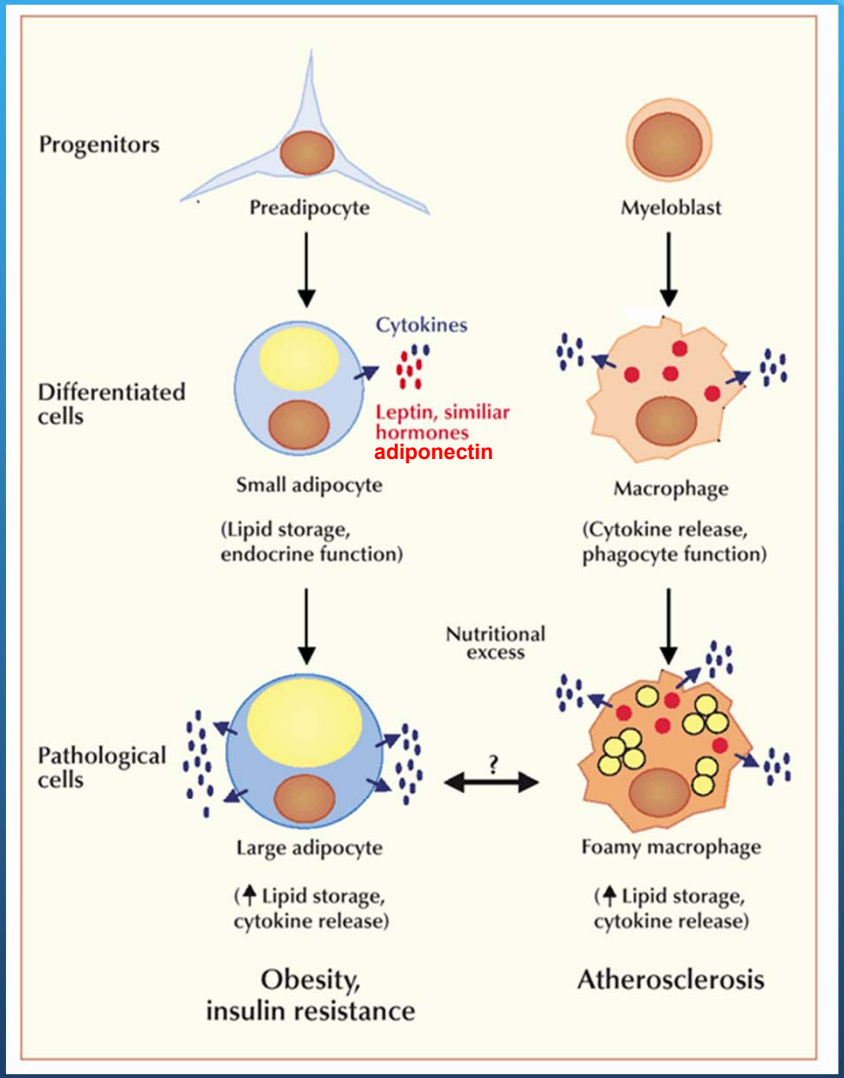
(Succinate dehydrogenase activity)

and reduces the size of the adipocytes



Luquet et al. Peroxisome proliferator-activated receptor delta controls muscle development and oxidative capability. *FASEB J*. 2003,17:2299-301

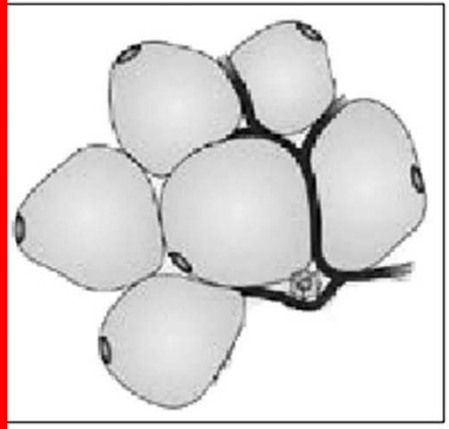
Convergence of macrophage and adipocyte functions in obesity and metabolic syndrome



Lehrke M et al. Nature Medicine 2004;10:355-61

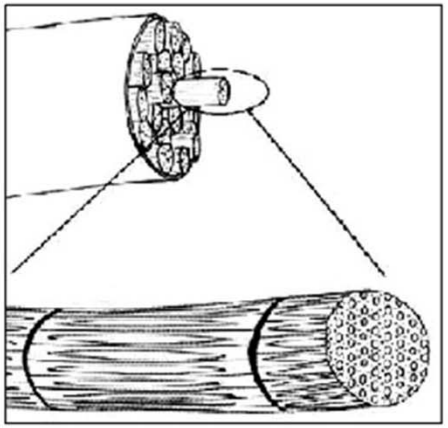
PPARβ actions on metabolism in adipose tissue, skeletal muscle, and heart

adipose tissue



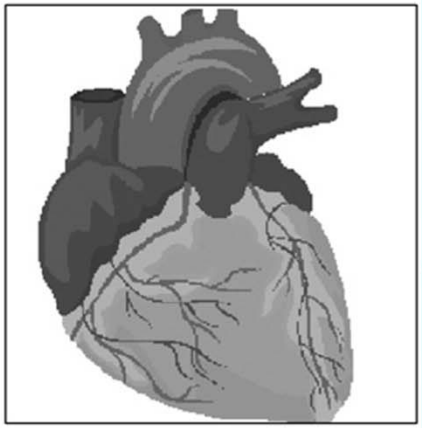
- adipocyte differentiation ↑
- gene expression for fatty acid oxidation ↑
- obesity resistance
- PPARβ activation → interleukin-6 ↓
- adipocyte interleukin-4/13 secretion → PPARβ in macrophages ↑ → antiinflammatory phenotype → insulin sensitivity ↑

skeletal muscle



- glucose oxidation ↓
- lipid utilisation, cholesterol efflux, energy uncoupling, β-oxidation ↑
- number of oxidative fibres ↑
- angiogenesis ↑
- myonuclear density ↑

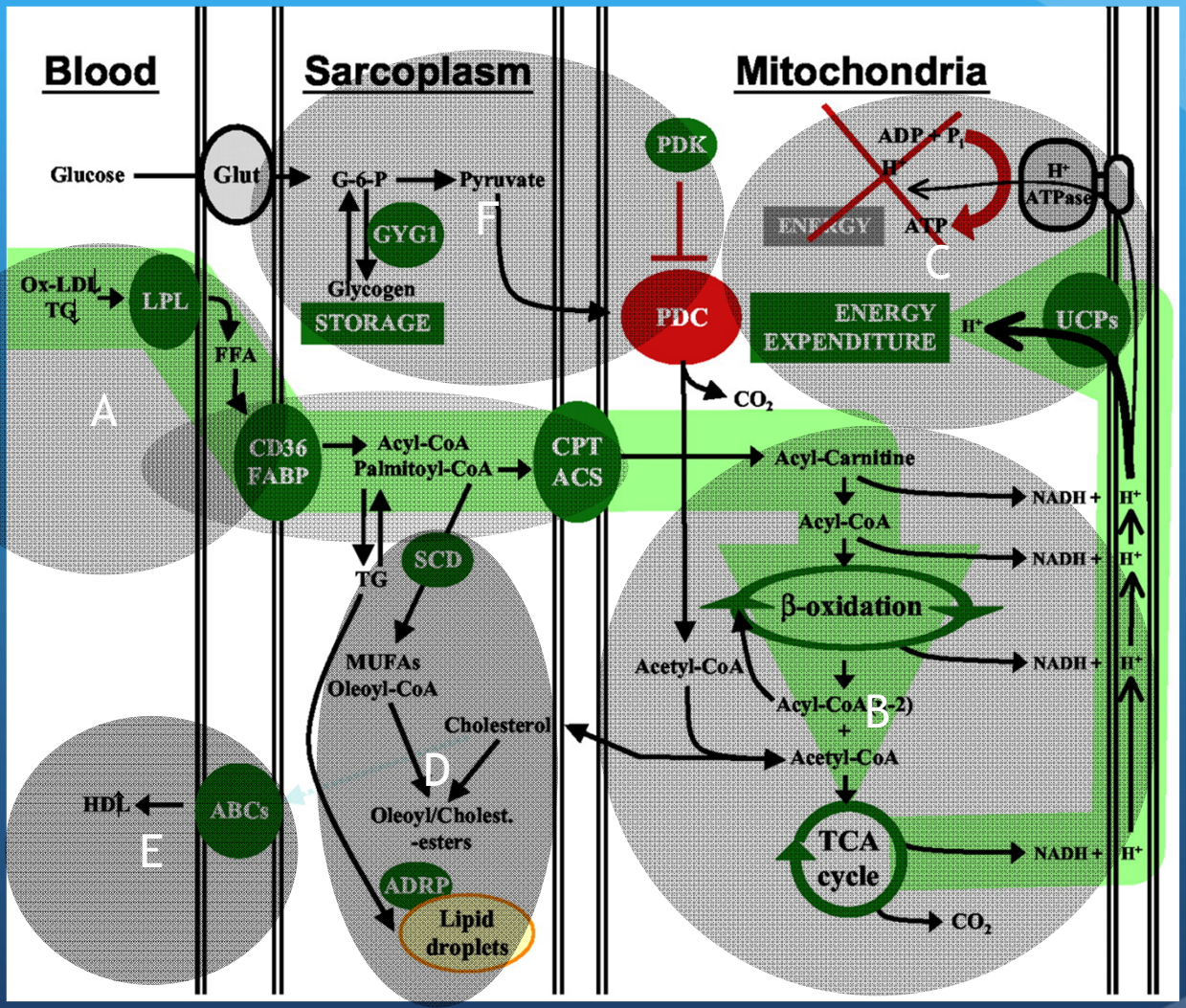
heart



- apoptosis (*in vitro*) ↓
- angiogenesis ↑
- cardiomyocyte growth ↑
- NFκB signalling ↓
- fatty acid oxidation ↑
- infarct size ↓
- fibrosis ↓

Wagner et al. Pharmacology & Therapeutics 2010;125: 423–435

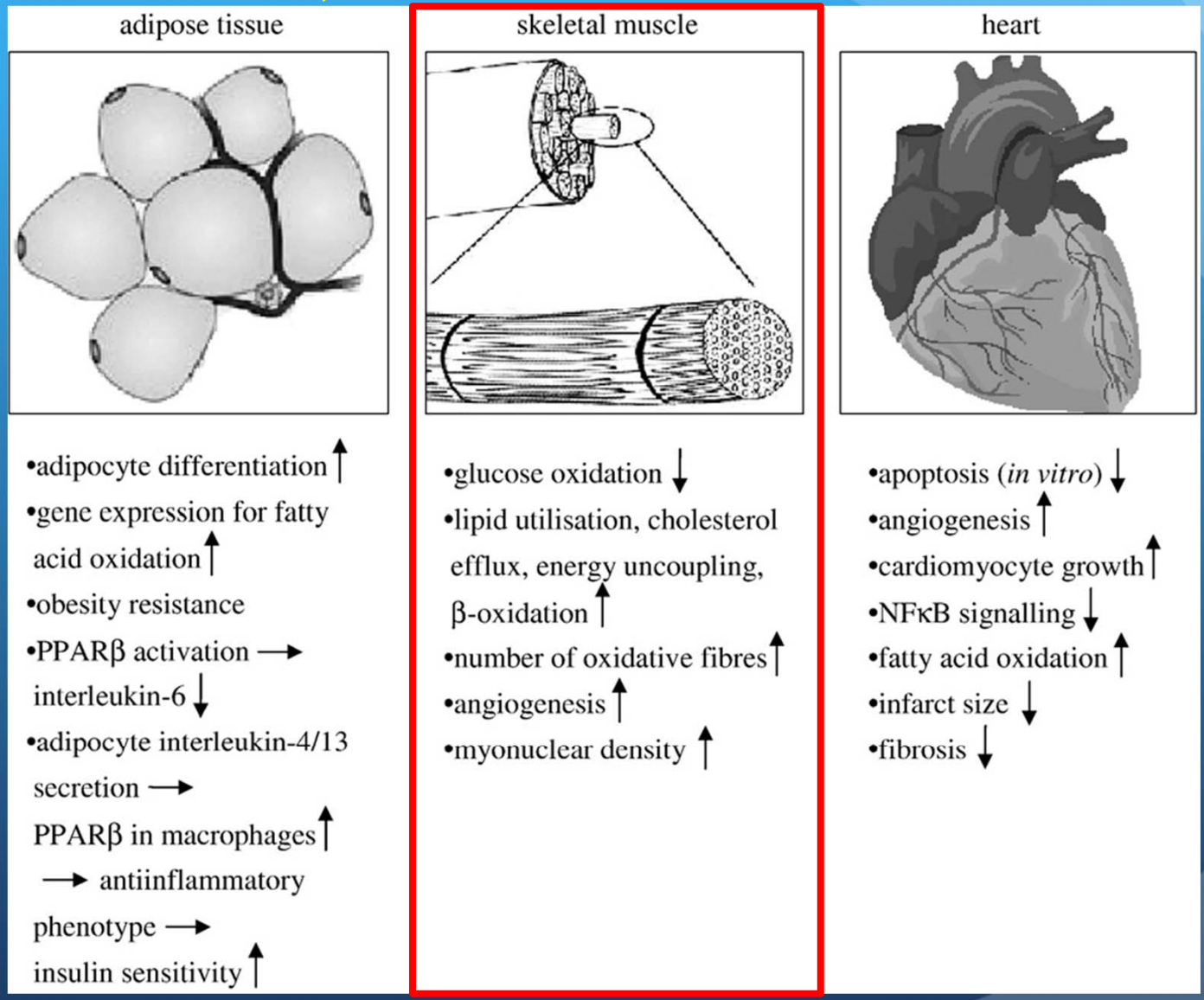
Metabolic PPARδ action in skeletal muscle



A:lipid uptake
B:lipid utilization
C:energy expenditure
D:lipid storage
E:cholesterol efflux
F:CHO catabolism

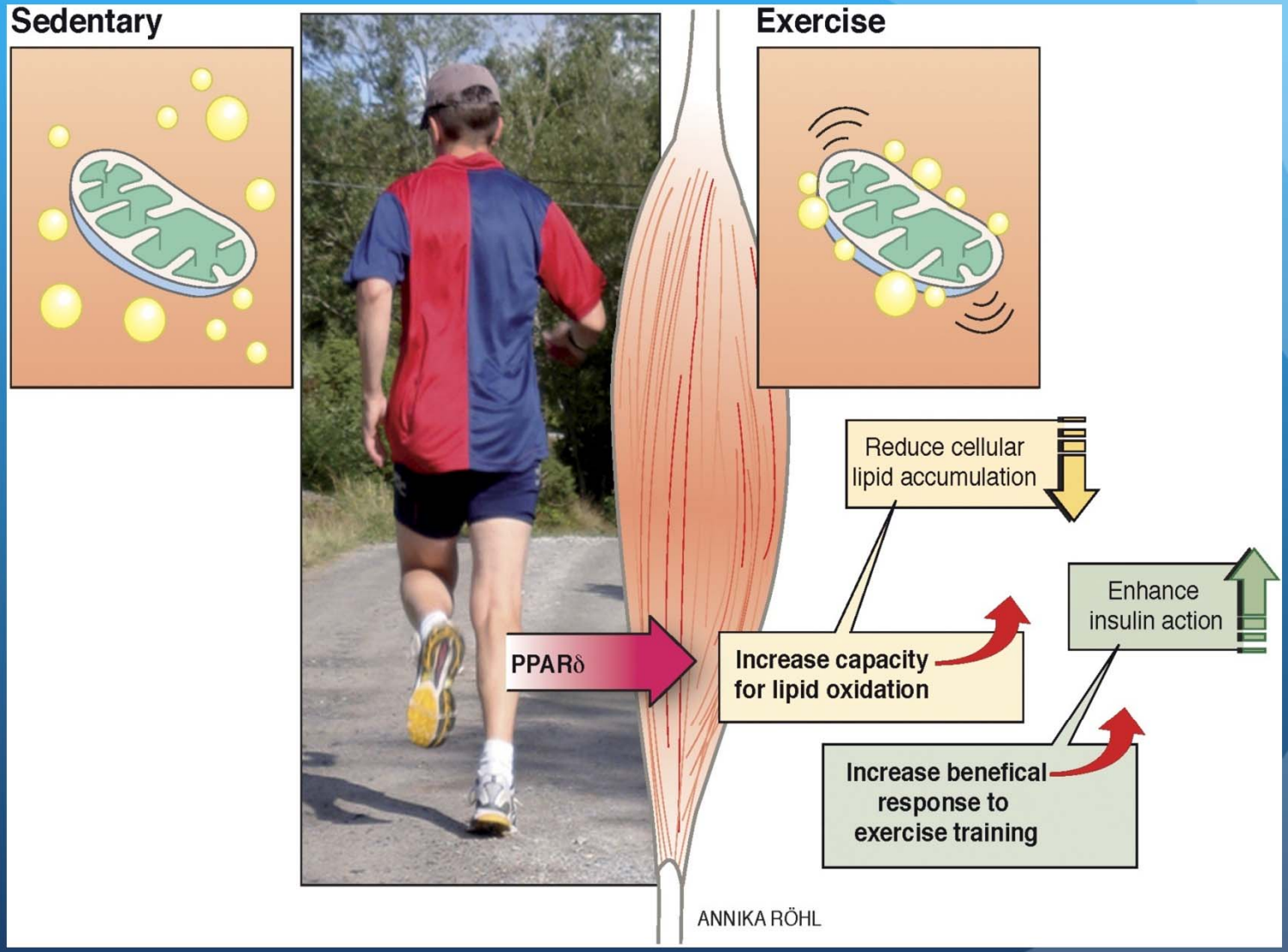
Dressel et al.Adv Molecu Cell Endocrine 2006;5:43–62

PPARβ actions on metabolism in adipose tissue, skeletal muscle, and heart



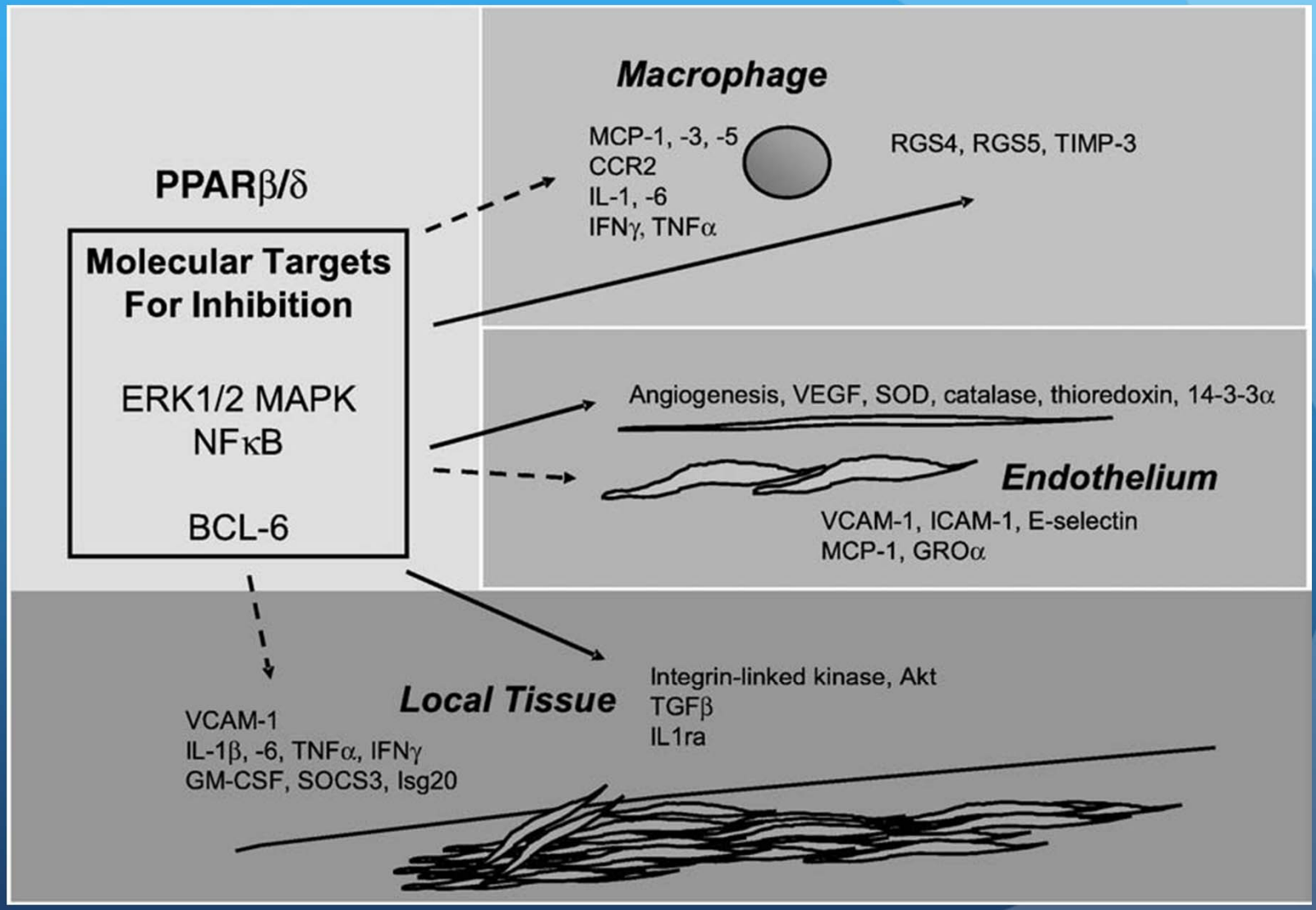
Wagner et al. Pharmacology & Therapeutics 2010;125: 423–435

Skeletal muscle responses to activation of PPARδ



Ehrenborg E et al. Pharmacol Rev 2009;61:373-93

Mechanisms of the anti-inflammatory effects of PPARß/δ



Bishop-Bailey D et al. Pharmacology & Therapeutics 2009;24:141–150

PPARβ actions on metabolism in adipose tissue, skeletal muscle, and heart

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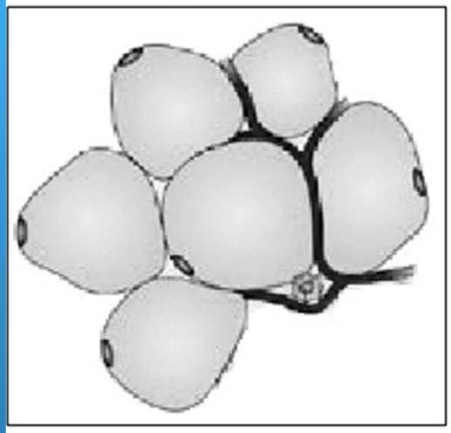

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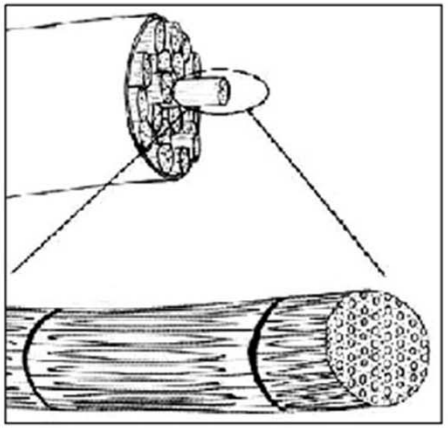

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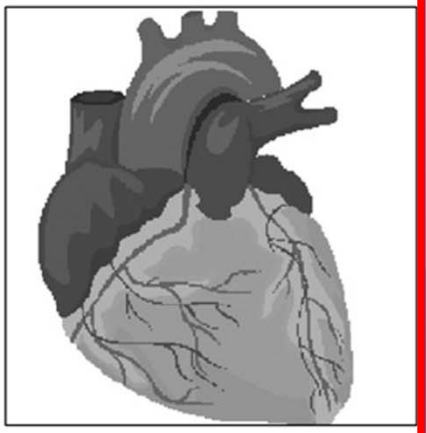
- myonuclear density ↑

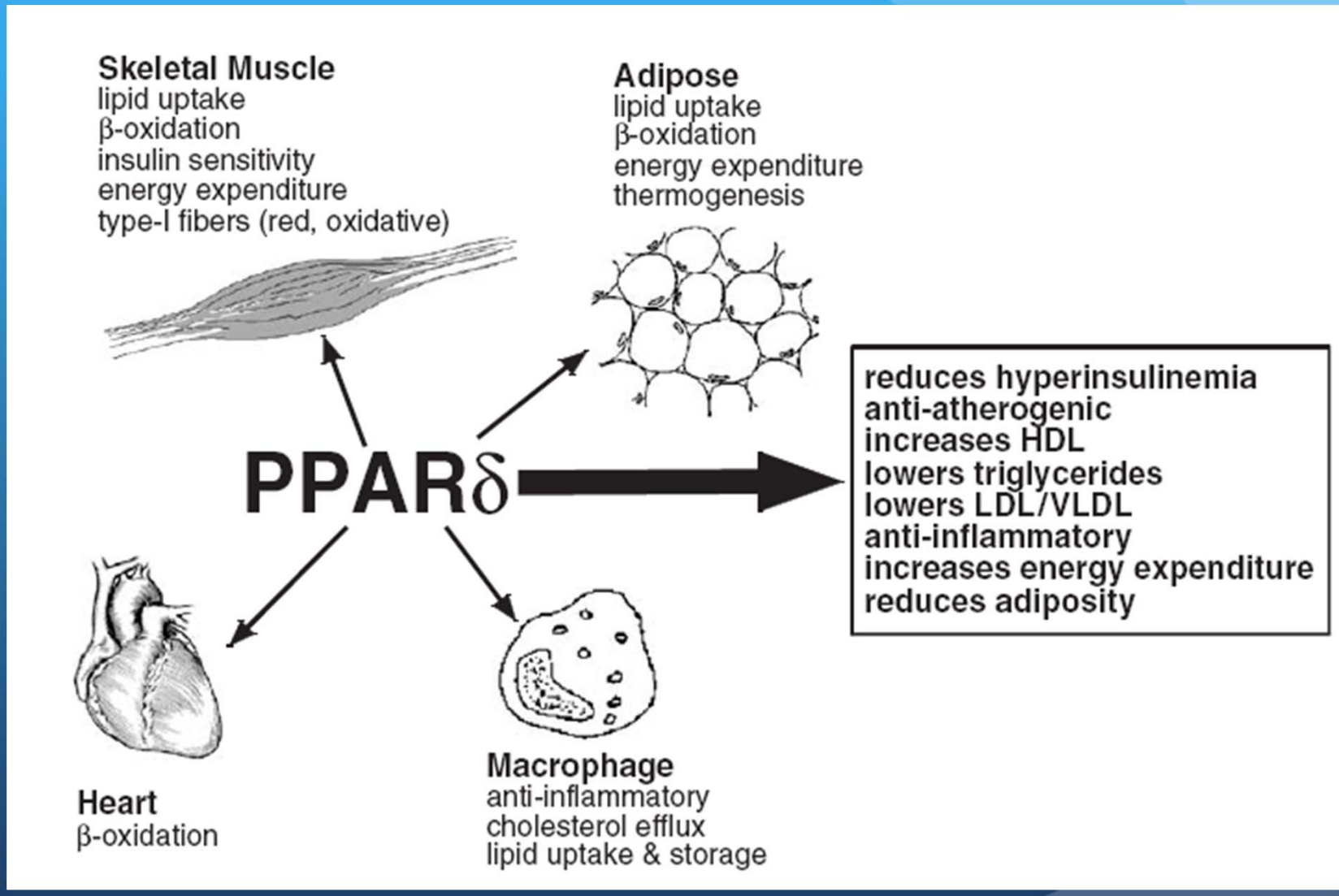
heart



- apoptosis (*in vitro*) ↓
- angiogenesis ↑
- cardiomyocyte growth ↑
- NFκB signalling ↓
- fatty acid oxidation ↑
- infarct size ↓
- fibrosis ↓

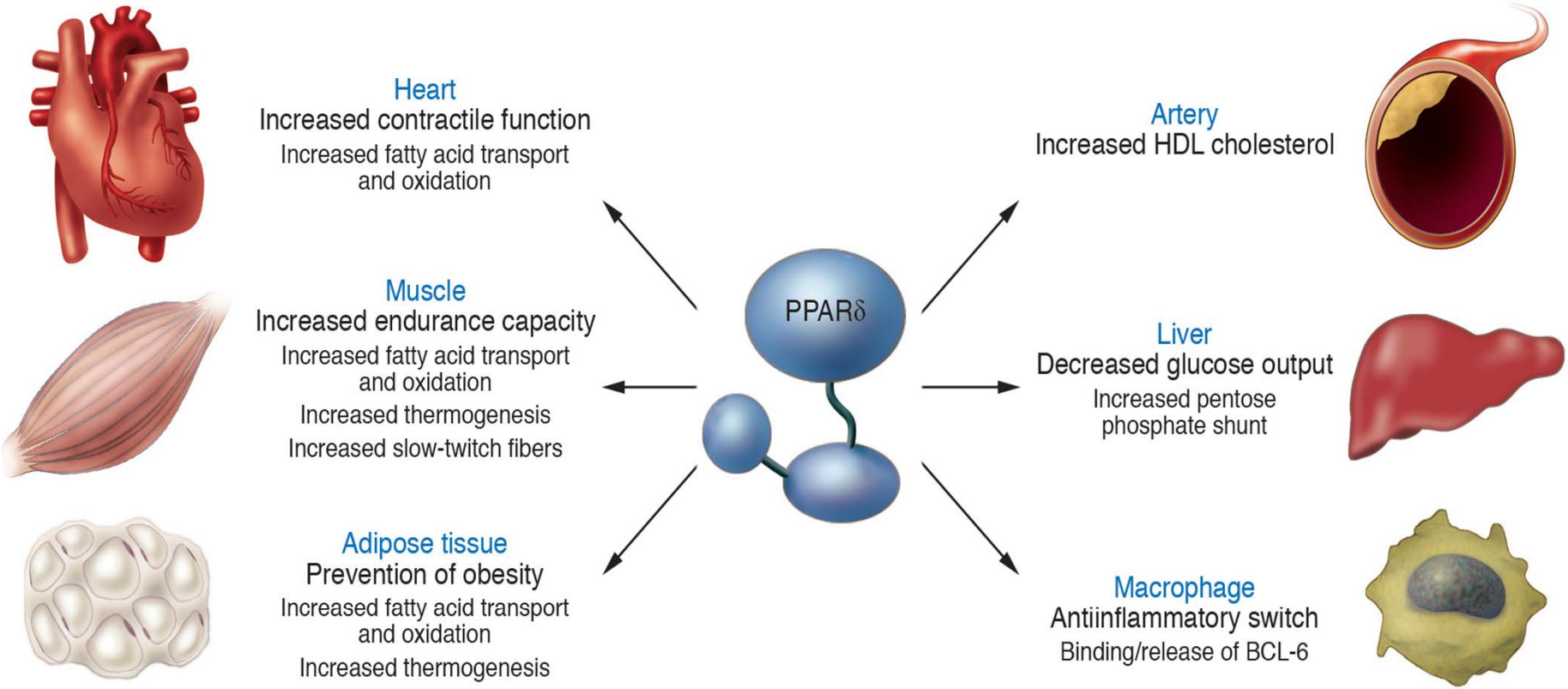
Wagner et al. Pharmacology & Therapeutics 2010;125: 423–435

Physiological Actions of PPARδ



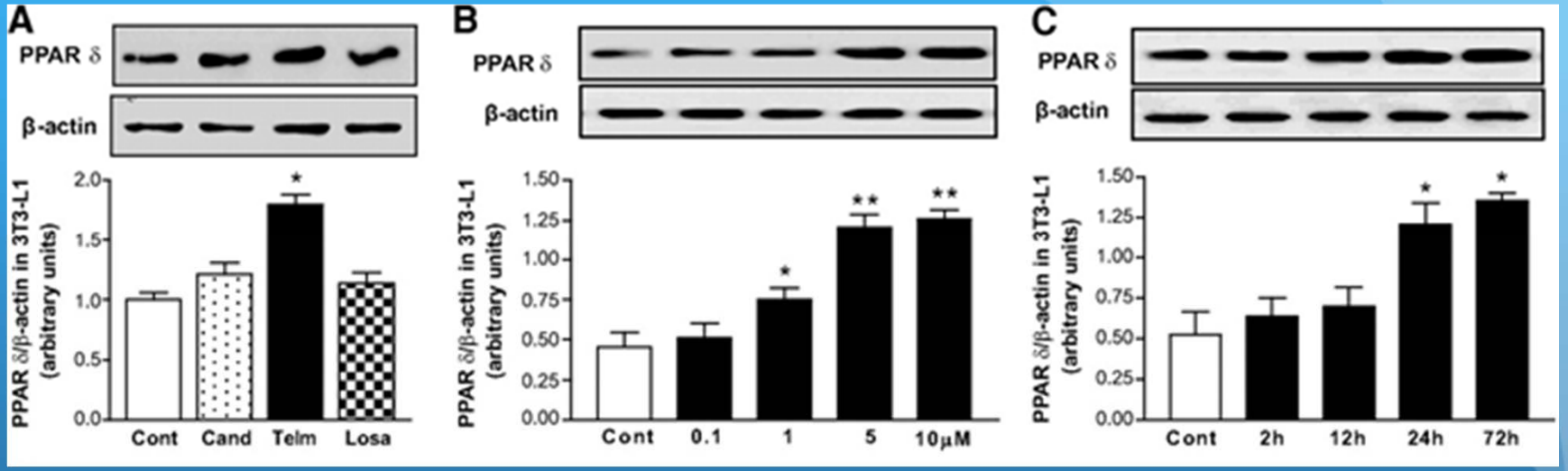
Dressel et al.Adv Molecu Cell Endocrine 2006;5:43–62

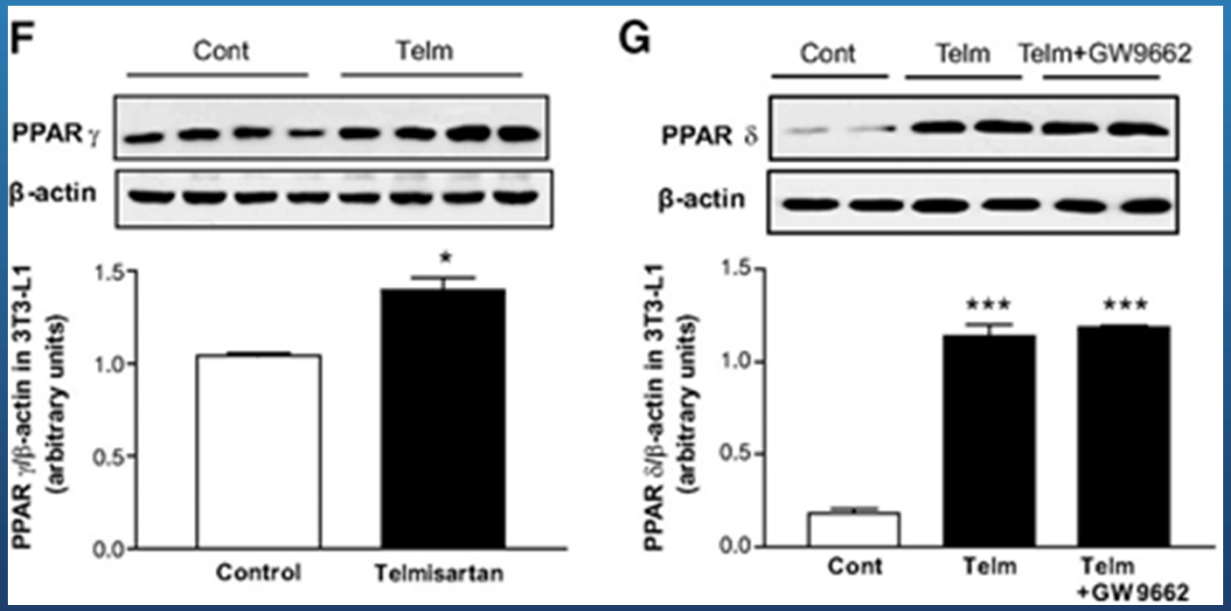
Therapeutic targets of PPARδ in the metabolic syndrome



Barish GD et al. J. Clin. Invest. 2006;116:590–597. doi:10.1172/JCI27955

Telmisartan activates PPARδ in 3T3-L1 preadipocytes

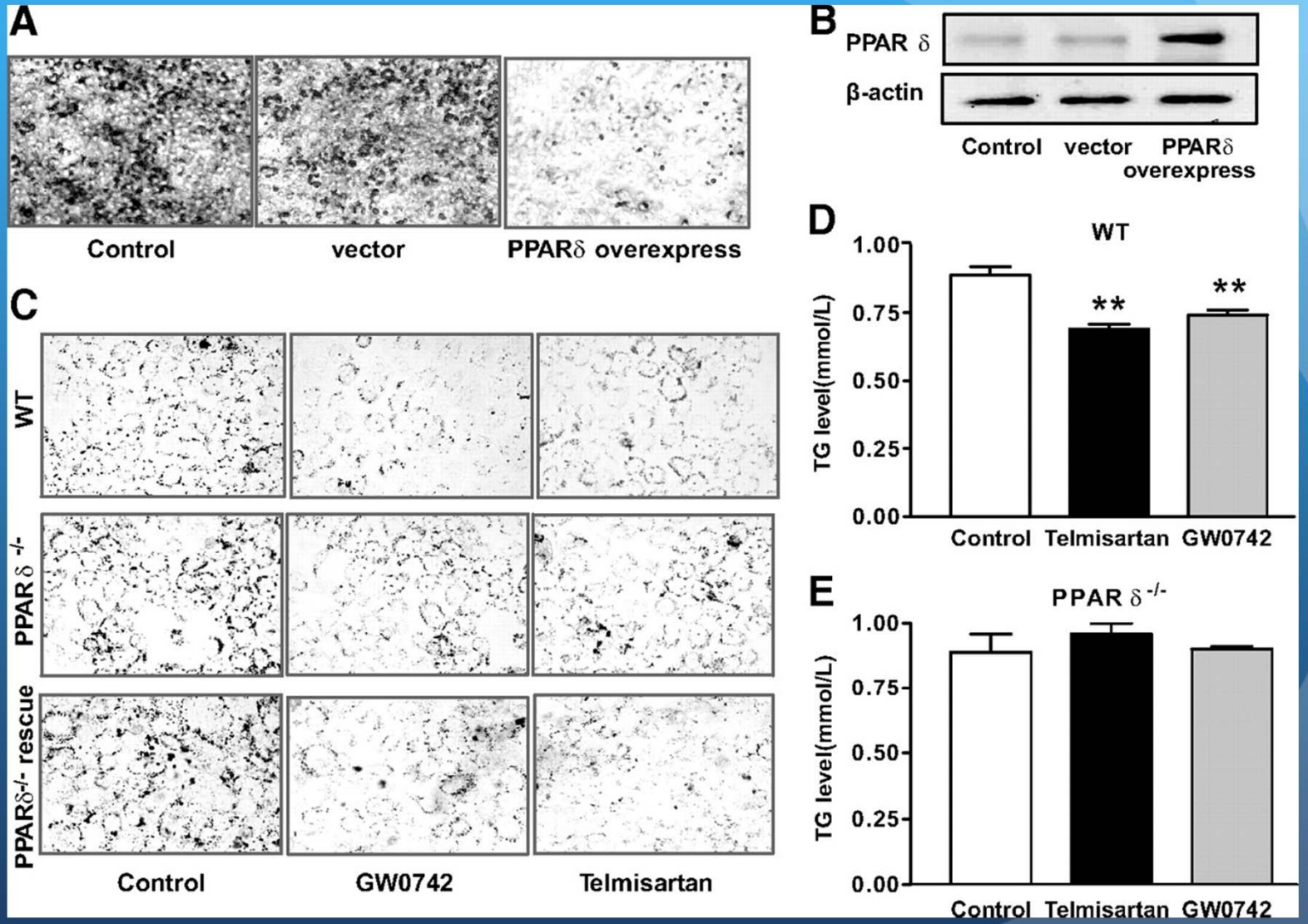




3T3–L1 preadipocytes
PC12W cells- AT1R knockout
GW9662: PPARγ- inhibitor
GW0742:selective PPARδ agonist

He, H. et al. Hypertension 2010;55:869-879

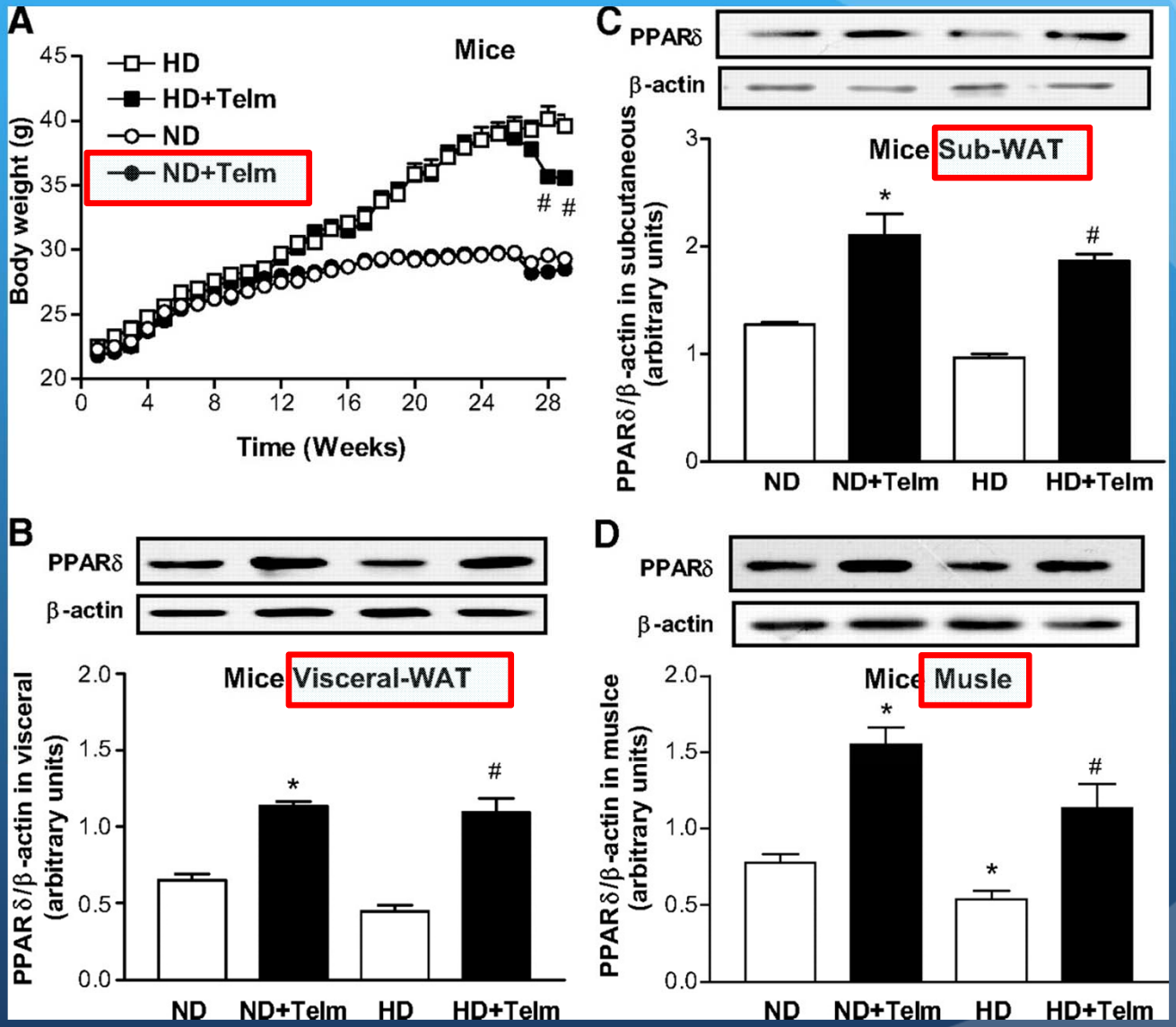
Effect of PPARδ overexpression or PPARδ activation on adipogenesis in adipocytes



GW0742:selective PPARδ agonist

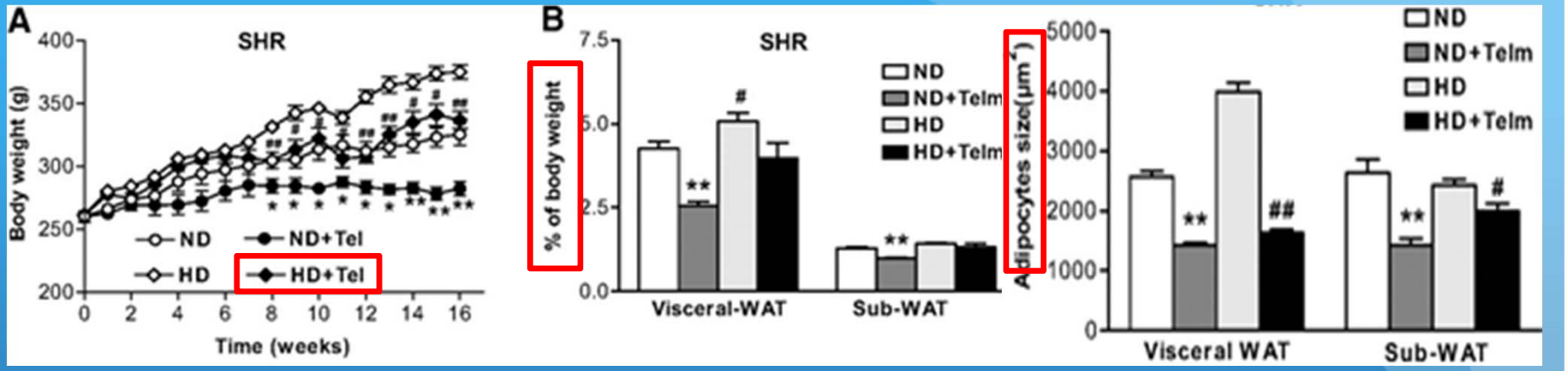
He, H. et al. Hypertension 2010;55:869-879

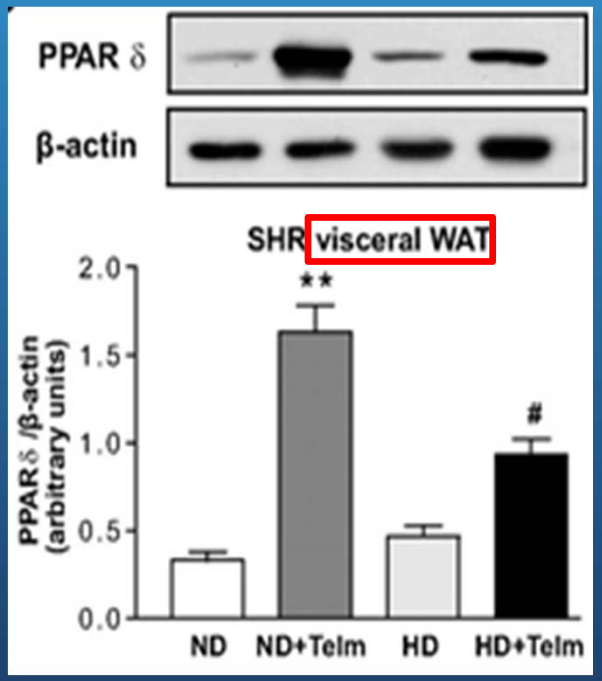
Effect of telmisartan on body weight and PPARδ expression in adipose tissue from wild-type mice

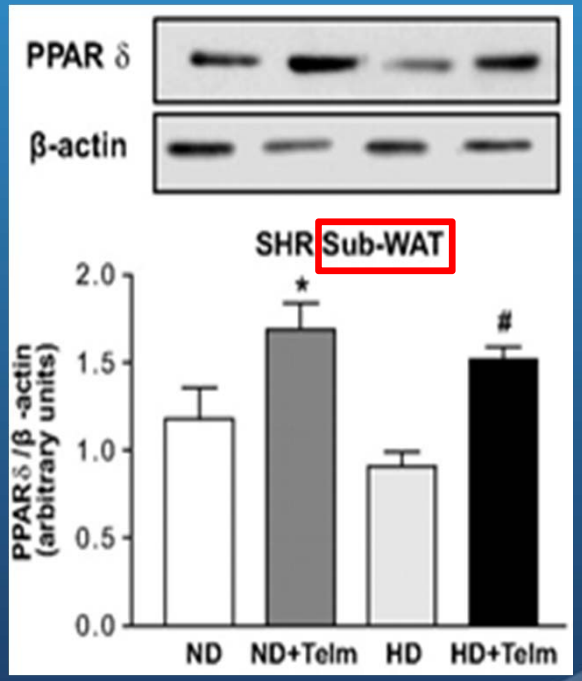


He, H. et al. Hypertension 2010;55:869-879

Effect of telmisartan on adipose tissue and PPARδ expression in SHRs

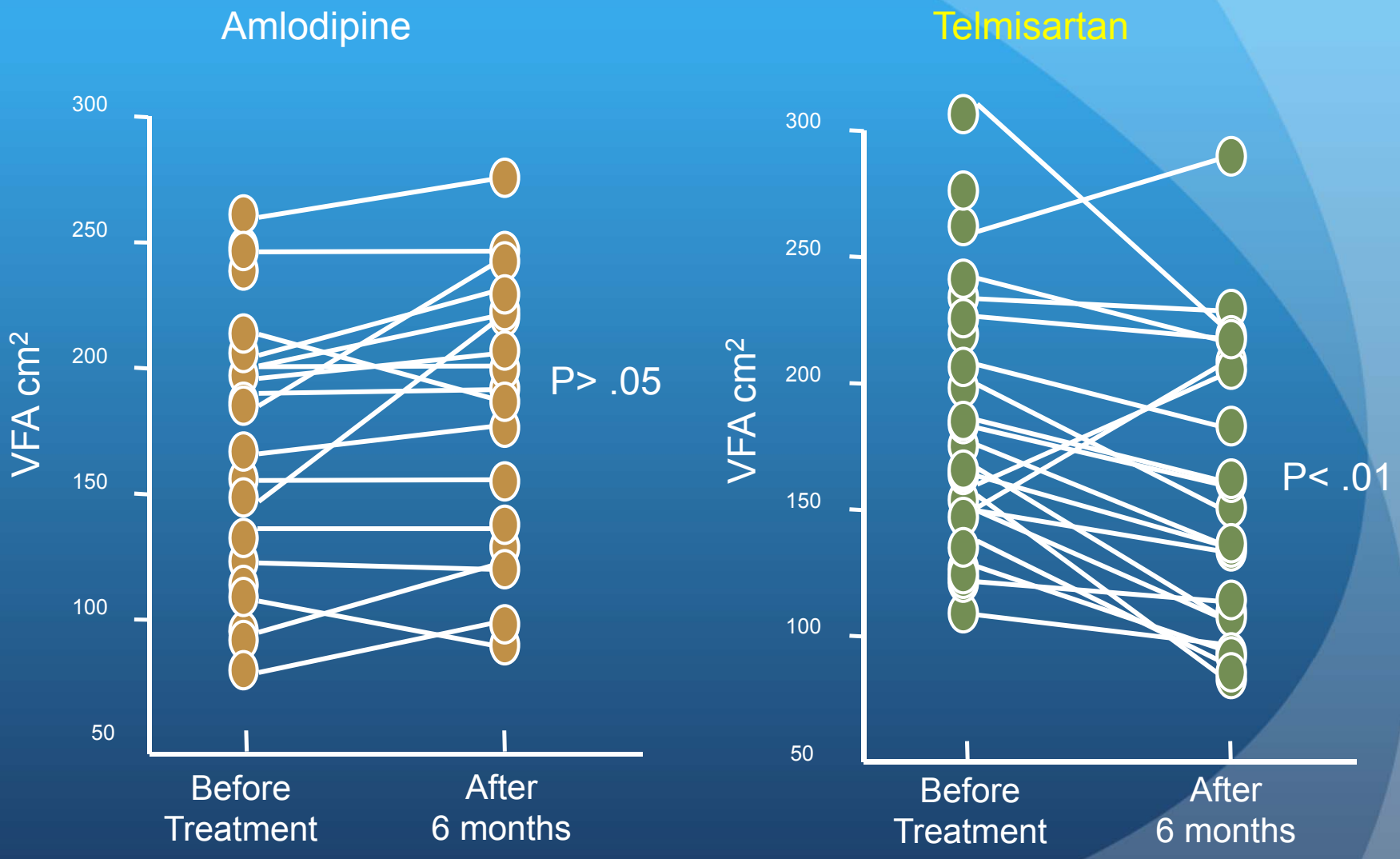






He, H. et al. Hypertension 2010;55:869-879

Changes in Visceral Fat



Shimabukuro et al. *J Hypertens.* 2007:25:841-848

Changes in HDL with Telmisartan

HDL	change	Before Telmi	After Telmi	p value (pared t-test)
		Mean ± SD	Mean ± SD	
HDL<40	↑	33.3 ± 4.9	37.7 ± 9.8	0.000
HDL≥40	→	51.6 ± 9.8	50.0 ± 9.8	0.021

Apo A1	change	Before Telmi	After Telmi	p value (pared t-test)
		Mean ± SD	Mean ± SD	
HDL<40	↑	102.5 ± 15.3	115.0 ± 22.9	0.002
HDL≥40	→	163.7 ± 24.6	140.6 ± 21.8	0.258

n=127, HDL<40mg/dL; n=302, HDL≥40
Follow-up interval: 15 ± 3 months

Unpublished data, Seo HS, 2011

Effect of telmisartan on Fat metabolism

- PPARγ activation : insulin sensitivity↑
- PPARδ activation :

  FFA oxidation↑ - lipolysis↑

  HSL activation, lipoprotein lipase activation

  UCP activation - energy uncoupleing - promotion of caloric expenditure

  Adiponectin↑, HDL↑

  Adipogenic activation- visceral adipocyte size ↓

  Reduction of body weight - VAT

He et al. Hypertension. 2010;55:869-879

Telmisartan is the only ARB indicated for CV protection in a broad range of CV high-risk pts

	Losartan	Eprosartan	Irbesartan	Olmesartan	Valsartan	Candesartan	Telmisartan
Hypertension	✔	✔	✔	✔	✔	✔	✔
- Treatment of renal disease	✔		✔				
- Prevention of stroke in LVH	✔						
CV high risk							✔
Atherothrombotic CV disease such as:							✔
- Coronary heart disease							✔
- Peripheral vascular disease							✔
- Stroke							✔
Type 2 diabetes with target organ damage							✔
Heart failure or LV dysfunction	(✔)*				✔	✔	

*Restricted label

Product information provided by EMA (http://www.emea.europa.eu) and eMC (http://emc.medicines.org.uk).

Conclusions

- There was no difference in effectiveness between asians and non-asians.
- Telmisartan is generally better tolerated than Ramipril.
- A higher proportion of Asians achieved the Full Dose of Telmisartan and Ramipril
- There were less discontinuations among Asians.
- Pleiotrophic action of Telmisartan – PPARγ & PPARσ

  - additional benefit for Metabolic Syndrome

감사합니다.