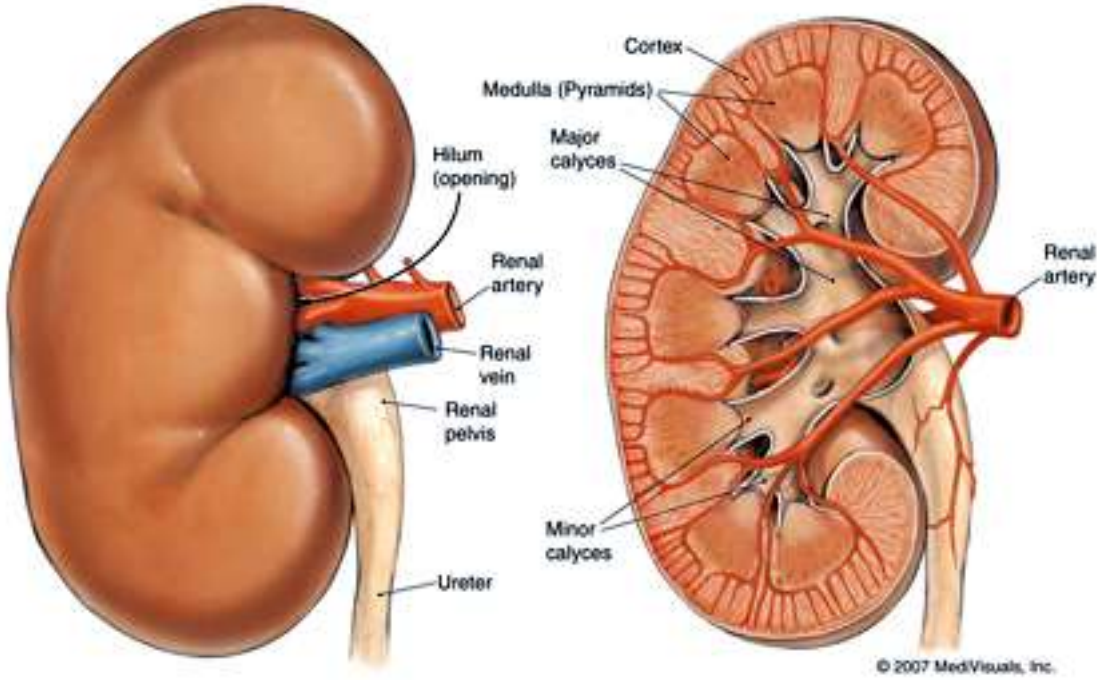
Chronic Kidney Disease as cardiovascular risk predictor
Evidence based clinical management



Fabio Mazza

- **CKD (Chronic Kidney Disease) is an ever-increasing clinical condition marked by a progressive reduction of kidney function.**

- **The primary causes of CKD are an ageing population and kidney complications due to systemic diseases such as arterial hypertension, type II diabetes mellitus, and dyslipidemia.**

J Am Soc Nephrol. 18 (4) (2007) 1246-1261

- **Many epidemiologic reports and controlled clinical trials suggest that dyslipidemia significantly worsen both renal progression and cardiovascular disease in this population.**

- **Epidemiologic Association between Dyslipidemia and CV Outcome in CKD**

- **The plasma lipid patterns change substantially as kidney disease progresse.**

***JAMA* 289: 1681–1690, 2003**

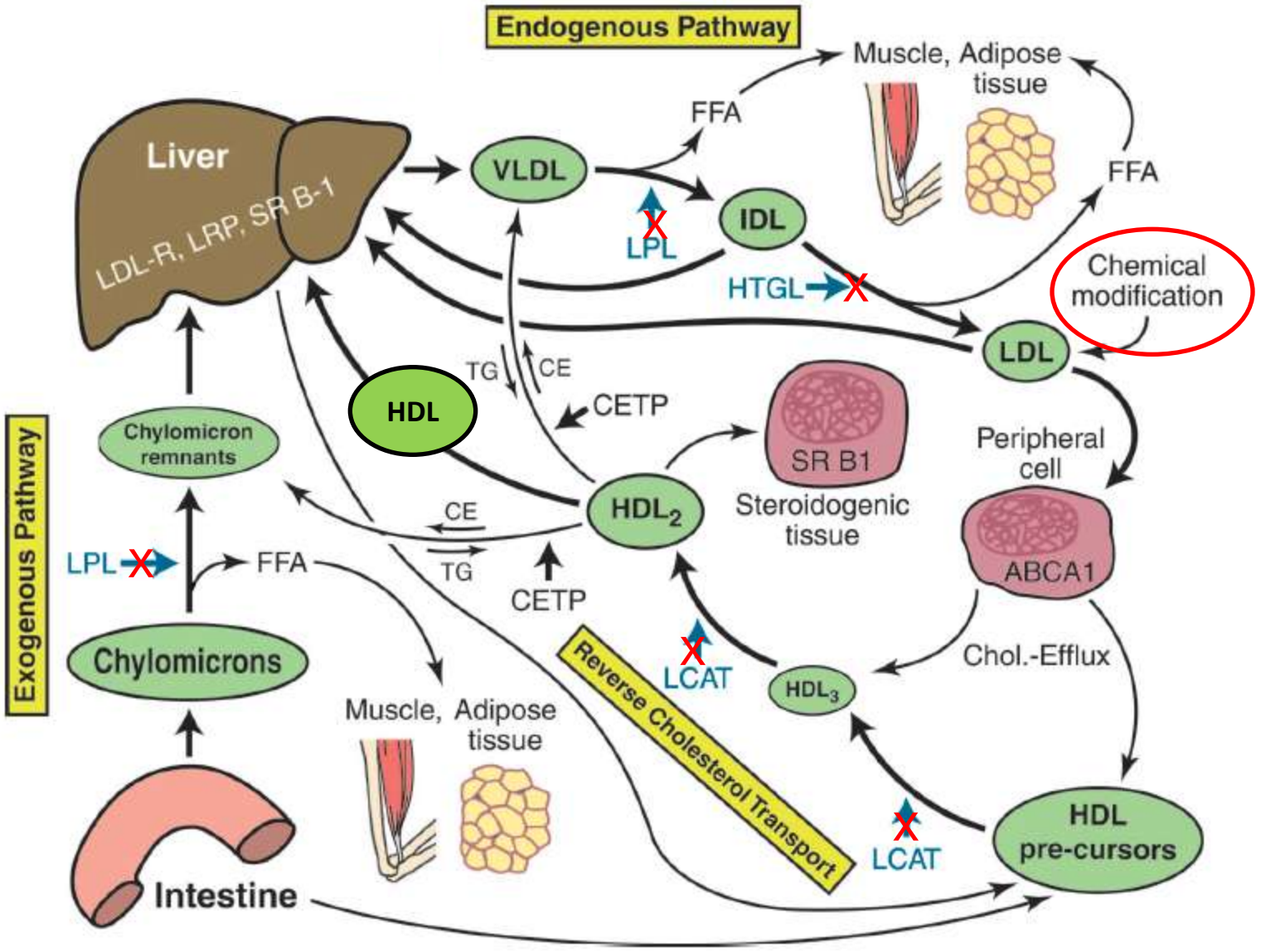
Trend of changes in lipids, lipoproteins in various stages of CKD

Parameter	CKD 1 to 5	Nephrotic Syndrome	Hemodialysis	Peritoneal Dialysis
Total cholesterol	↗	↑ ↑	↔ ↓	↑
LDL cholesterol	↗	↑ ↑	↔ ↓	↑
HDL cholesterol	↓	↓	↓	↓
Non–HDL cholesterol	↗	↑ ↑	↔ ↓	↑
TG	↗	↑ ↑	↑	↑
Lp(a)	↗	↑ ↑	↑	↑ ↑

The lipid profile in the majority of patients with CKD is characterized by both quantitative and qualitative changes in circulating lipoproteins.

TG (triglycerides) are often elevated due to a deficit in the catabolism of triglyceride-rich lipoproteins

***J Am Soc Nephrol* 18: 1246–1261, 2007.**


Endogenous Pathway
Muscle, Adipose tissue
FFA
Liver
LDL-R, LRP, SR B-1
VLDL
IDL
LPL
HTGL
FFA
Chemical modification
LDL
TG
CE
CETP
HDL
Chylomicron remnants
SR B1
Steroidogenic tissue
Peripheral cell
HDL2
CE
TG
CETP
ABCA1
Exogenous Pathway
LPL
FFA
Chylomicrons
LCAT
HDL3
Chol.-Efflux
Reverse Cholesterol Transport
Muscle, Adipose tissue
LCAT
HDL pre-cursors
Intestine

- **Reduced lipolytic activity either by HL (hepatic lipase) adipose tissue LPL (lipoproteinlipase)**
- **Factors related to the uremic syndrome (uremic toxins)**
- **Peripheral tissue resistance to insulin**
- **Secondary hyperparathyroidism**
- **Frequent heparinization**
- **Other plasma lipase inhibitor**

Cryer A: Tissue lipoprotein lipase activity and its action in lipoprotein metabolism.
***Int J Biochem* 13: 525–541, 1981**

Daily therapy in a patient with Chronic Kidney Disease

1. Ace inhibitor
2. Sartans
3. Calcium antagonist
4. Vitamin D
5. Calcium carbonate
6. Iron
7. Folic Acid supplementation
8. Erythropoietin
9. Other drugs

Hypertension

Calcium Phosphorus Metabolism

Anemia
Normocytic / Normochronic
Treatment

Poor Compliance for Lipid-Lowering Drug

- **A non-pharmaceutical but nutraceutical treatment for lipid-lowering therapy**

- **Monascus purpureus–Linear aliphatic alcohols–Niacin (Dif1stat®)**

- **The hypocholesterolemic efficacy of MP was evaluated through experimental and clinical trials.**

- **By acting through the direct inhibition of 3-hydroxy-3-methylglutaryl coenzymeA reductase.**

A new hypocholesterolemic agent that specifically inhibits 3-hydroxy-3-methylglutaryl coenzyme A reductase, J Antibiot. 33 (3) (1980) 334-336.

Lipids
DOI 10.1007/s11745-009-3368-5

ORIGINAL ARTICLE

Combined Treatment with Dif1stat® and Diet Reduce Plasma Lipid Indicators of Moderate Hypercholesterolemia More Effectively than Diet Alone: A Randomized Trial in Parallel Groups

Claudia Stefanutti · Fabio Mazza · Antonio Vivenzio · Serafina Di Giacomo · Giuseppina Perrone · Mariarosaria Serra · Antonello Bucci

Received: 30 June 2009 / Accepted: 17 September 2009

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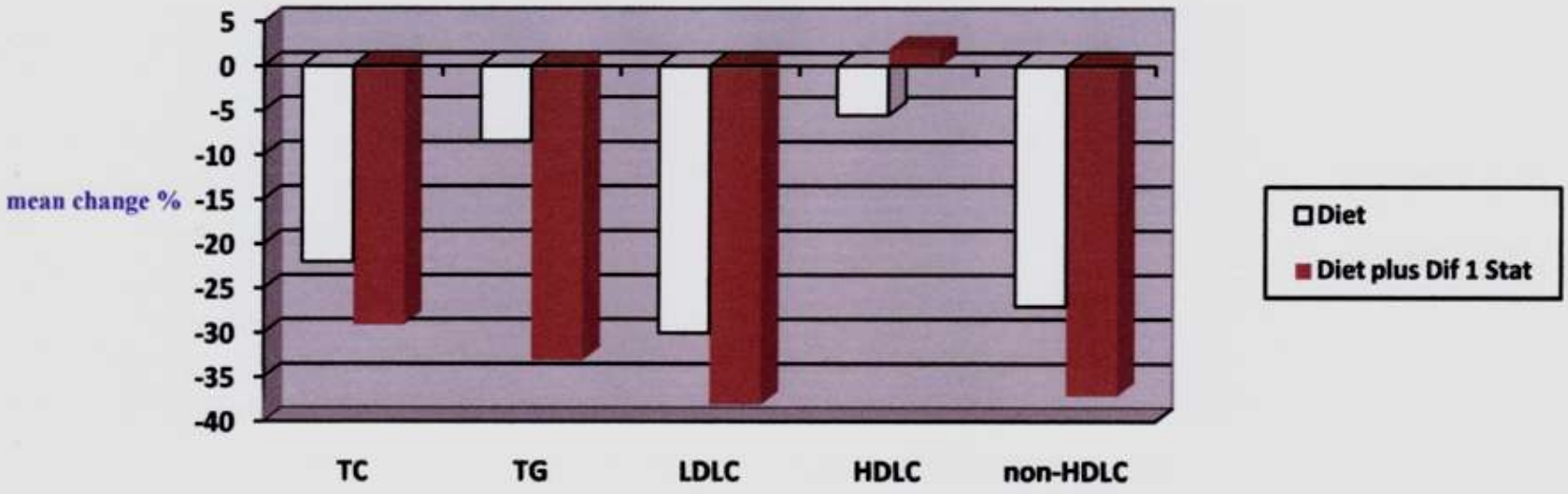
UMBERTO I
POLICLINICO DI ROMA

ORIGINAL ARTICLE

Combined Treatment with Dif1stat® and Diet Reduce Plasma Lipid Indicators of Moderate Hypercholesterolemia More Effectively than Diet Alone: A Randomized Trial in Parallel Groups

Mean change in plasma (TC), triglycerides (TG), low-density lipoprotein-cholesterol (LDLC), high-density lipoprotein-cholesterol (HDLC) and non-HDLC levels, in patients with mild hypercholesterolemia after 8 months (T2) of treatment with Diet and Diet plus Dif 1Stat



Δ%	-30%	-33%	-38%		-37%

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Efficacy and Safety of Dif1stat® for the Treatment of Secondary Dyslipidemia in Chronic Kidney Disease

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Material and Methods

Table 1 Patient demographics.

Patients (# 1104) groups	Male, 65% (# 717)	Female, 35% (# 387)	Age (70 ± 11), years ± SD	Stage of CKD	GFR, mL/min/1.73m^2
A (180)	61.1% (110)	38.8% (70)	69 ± 10	II°	67 ± 16
B (744)	69% (514)	31% (230)	70 ± 13	III°	38 ± 12
C (180)	51.6% (93)	48.3% (87)	71.8 ± 11	IV°	19 ± 6

Exclusion Criteria

- **No patient exhibited hematologic, hepatic, thyroid or neoplastic diseases.**
- **Patients with cardiac disease, patients with proteinuria due to nephrotic and nephritic syndromes as well as diabetes, were excluded.**
- **None of the patients were given drugs to treat metabolic/lipid disorders, beta-blockers, diuretics, corticosteroids.**

Laboratory

- **LDLC plasma cholesterol was calculated using the Friedewald formula: LDLC = TC - (HDLC - TG/5)**
- **Non-HDLC cholesterol was calculated using the non-HDLC = TC – HDLC**
- **GFR was calculated using CKD-EPI (The Chronic Kidney Disease Epidemiology Collaboration) Creatinine Equation: Creatinine, Age, Sex, Race.**

A New Equation to Estimate Glomerular Filtration Rate. Ann Intern Med **150(9):604-12. (2009)**

Table 2 Group A: Stage II of CKD according to KDOQI classification.

Months	T0	T6	Δ%	*P*	T12	Δ%	*P*	T18	Δ%	*P*	T24	Δ%	*P*
TC	251.4 ± 41	212 ± 23	-15.6	n.s	196.2 ± 39	-22	0.001	186 ± 62	-26	0.001	172 ± 83	-31	0.001
HDLC	46 ± 12	48 ± 16	4.3	n.s	50 ± 21	8.6	n.s	51 ± 18	10.8	n.s	52 ± 35	13	n.s
TG	152 ± 46	120 ± 75	-21	0.001	106 ± 45	-30	0.001	98 ± 61	-35	0.001	96 ± 40	-36.8	0.001
LDLC	175 ± 38	140 ± 47	-20	0.001	125 ± 52	-28	0.001	115 ± 62	-34	0.001	101 ± 51	-42	0.001
non-HDLC	205 ± 23	164 ± 41	-20	0.001	146 ± 19	-29	0.001	135 ± 26	-34	0.001	120 ± 31	-41	0.001
TC/HDLC	5.4	4.4	-19	n.s	3.9	-28	0.001	3.6	-33	0.001	3.3	-40	0.001
GFR	67 ± 16	67.2 ± 14	0.3	n.s	68 ± 17	1.2	n.s	68.5 ± 16	2.23	0.001	68.7 ± 12	2.5	0.001
Albuminuria	negative	negative	n/a	n/a	negative	n/a	n/a	negative	n/a	n/a	negative	n/a	n/a

180 patients with GFR (glomerular filtration rate) calculated at 67 ± 16 mL/min/m².

The percent variation (Δ%) and mean changes (mg/dL ± SD) in plasma lipid and lipoprotein profile and GFR, at baseline (T0), after 6 (T6), 12 (T12), 18 (T8) and 24 (T24) months treatment with Difl stat®.

HDLC: high density lipoprotein-cholesterol; LDLC: low-density lipoprotein-cholesterol; TC: total cholesterol; non-HDLC: non high density lipoprotein-cholesterol; TG: triglycerides; n.s = not significant; n/a = not applicable; *P* value ≤ 0.001.

Group A

Stage II of CKD according to KDOQI classification.
180 patients with glomerular filtration rate (GFR) calculated at 67 ± 16 mL/min/1.73m.²
The percent variation (Δ%) in plasma of non- high density lipoprotein cholesterol (non-HDLC) and TC/HDLC in patients with secondary dyslipidemia, after 6 (T6), 12 (T12), 18 (T8) and 24 (T24) months treatment with Dif1stat ®
*** P ≤ 0.001**

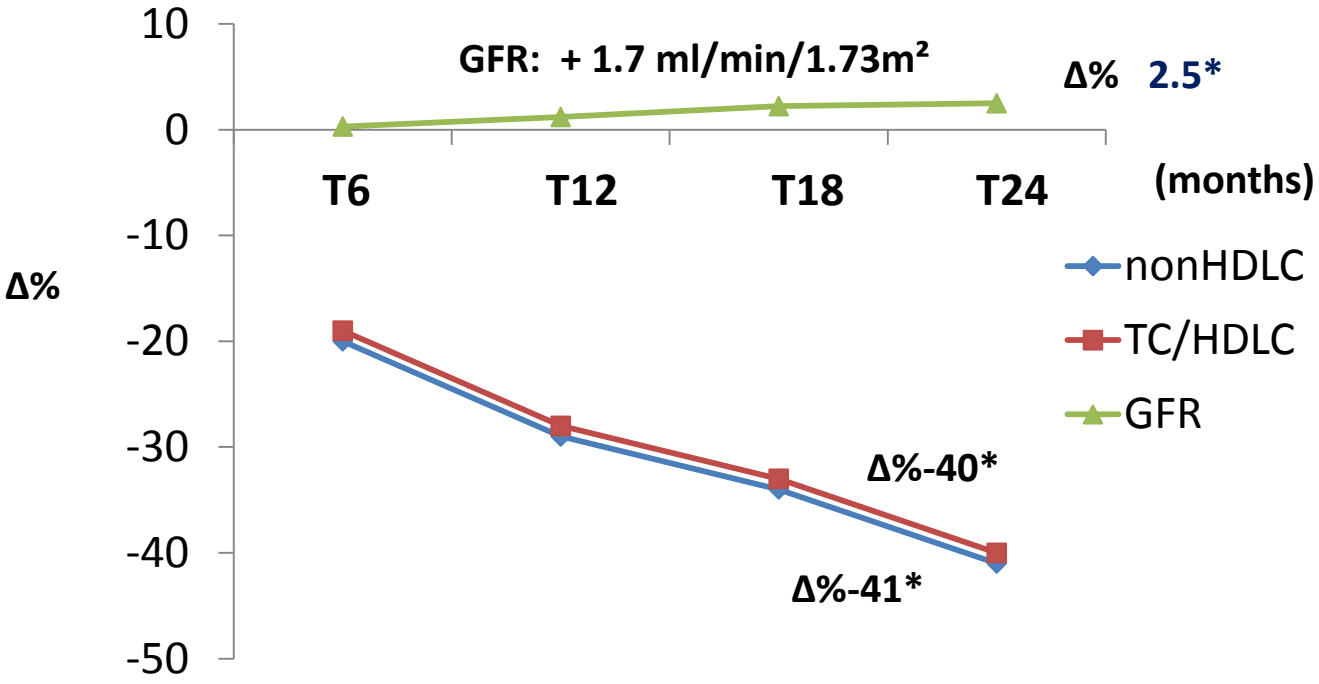


Table 3 Group B: Stage III of CKD according to KDOQI classification.

Months	T0	T6	Δ%	*P*	T12	Δ%	*P*	T18	Δ%	*P*	T24	Δ%	*P*
TC	269.8 ± 65	249.8 ± 73	-7.4	n.s	232 ± 59	-14	n.s	218 ± 46	-19	n.s	195.2 ± 81	-27	0.001
HDLC	42 ± 19	42.4 ± 22	0.95	n.s	43 ± 24	2.38	n.s	43.2 ± 31	2.9	n.s	43.5 ± 47	3.5	n.s
TG	184 ± 99	162 ± 152	-12	n.s	147 ± 90	-20	0.001	131 ± 103	-28	0.001	125 ± 94	-32	0.001
LDLC	190 ± 48	174 ± 94	-8.4	n.s	156 ± 56	-18	n.s	148 ± 71	-22	0.001	126 ± 34	-33	0.001
non-HDLC	227.8 ± 52	207.4 ± 44	-8.9	n.s	189 ± 39	-17	n.s	174.8 ± 63	-23.2	0.001	151.7 ± 33	-33.4	0.001
TC/HDLC	6.42	5.89	-8.2	n.s	5.39	-16	n.s	5.04	-21.4	0.001	4.48	-30	0.001
GFR	38 ± 12	38.1 ± 16	0.26	n.s	38.5 ± 17	1.31	0.001	38.6 ± 16	1.57	0.001	38.8 ± 11	2.1	0.001
Albuminuria	negative	negative	n/a	n/a	negative	n/a	n/a	negative	n/a	n/a	negative	n/a	n/a

744 patients with GFR (glomerular filtration rate) calculated at 38 ± 12 mL/min/m^2.

The percent variation (Δ%) and mean changes (mg/dL ± SD) in plasma lipid and lipoprotein profile and GFR, at baseline (T0), after 6 (T6), 12 (T12), 18 (T8) and 24 (T24) months treatment with Difl stat®.

HDLC: high density lipoprotein-cholesterol; LDLC: low-density lipoprotein-cholesterol; TC: total cholesterol; non-HDLC: non high density lipoprotein-cholesterol; TG: triglycerides; n.s = not significant; n/a = not applicable; *P* value ≤ 0.001.

Group B

Stage III of CKD according to KDOQI classification.

744 patients with glomerular filtration rate (GFR) calculated at 38 ± 12 mL/min/1.73m.²

The percent variation (Δ%) of plasma non- high density lipoprotein cholesterol (non-HDLC) and TC/HDLC in patients with secondary dyslipidemia, after 6 (T6), 12 (T12), 18 (T8) and 24 (T24) months treatment with Dif1stat ®

*** P ≤ 0.001**

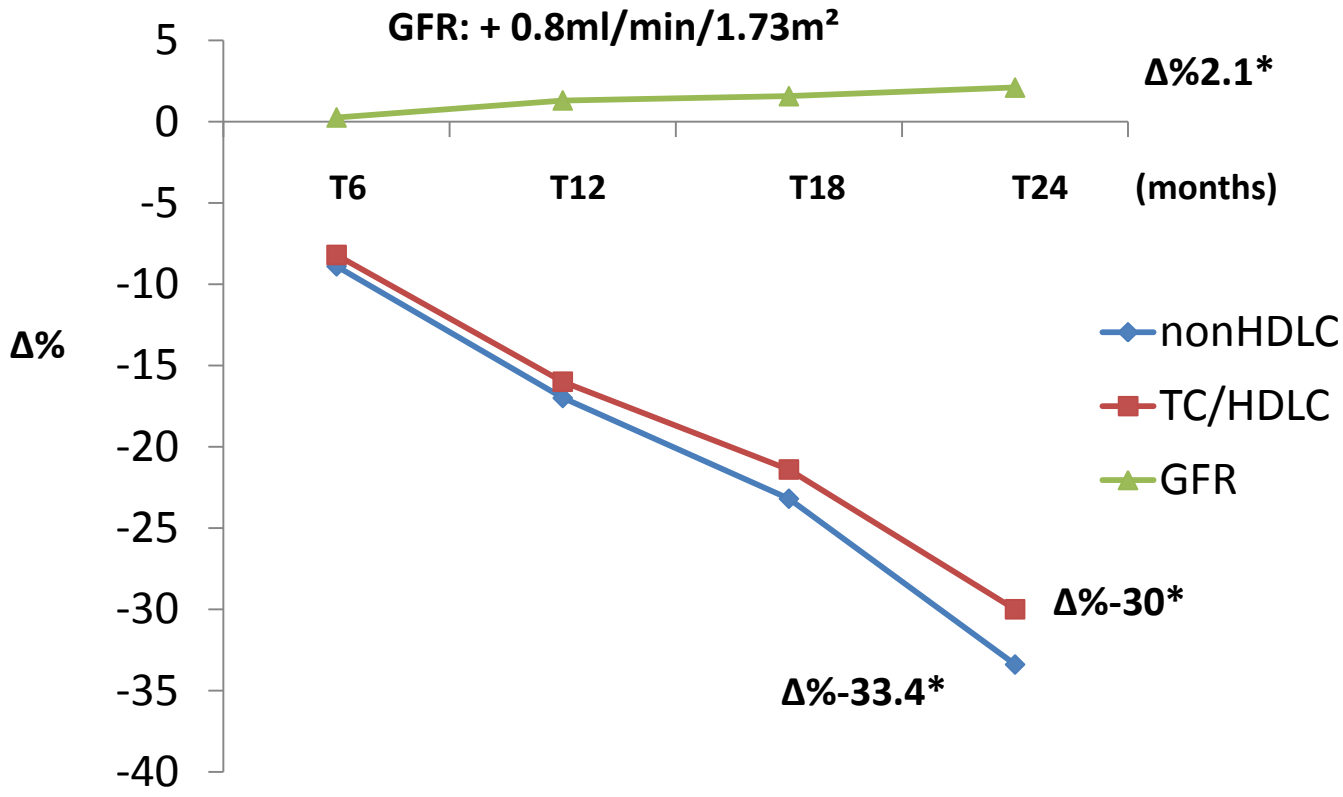


Table 4 Group C: Stage IV of CKD according to KDOQI classification.

Months	T0	T6	Δ%	*P*	T12	Δ%	*P*	T18	Δ%	*P*	T24	Δ%	*P*
TC	285 ± 57	251 ± 29	-12	n.s	219 ± 32	-23	0.001	210 ± 41	-26	0.001	193.4 ± 53	-32	0.001
HDLC	35 ± 19	31 ± 16	-11	n.s	36 ± 22	2.8	n.s	38.2 ± 29	9.1	n.s	39.8 ± 18	13	n.s
TG	222 ± 57	186 ± 63	-16	n.s	152 ± 41	-31	0.001	141 ± 59	-36	0.001	137 ± 39	-38	0.001
LDLC	196 ± 71	173 ± 96	-11.7	n.s	151 ± 85	-23	0.001	143 ± 94	-27	0.001	126 ± 45	-35	0.001
non-HDLC	250 ± 33	220 ± 42	-12	n.s	183 ± 67	-26.8	0.001	171.8 ± 49	-31.8	0.001	153 ± 56	-38.5	0.001
TC/HDLC	8.14	8	-0.56	n.s	6.08	-25.2	0.001	5.49	-32.4	0.001	4.85	-40	0.001
GFR	19 ± 6	19.1 ± 5	0.52	n.s	19.25 ± 7	1.31	0.001	19.38 ± 2	2	0.001	19.42 ± 1	2.1	0.001
Albuminuria	negative	negative	n/a	n/a	negative	n/a	n/a	negative	n/a	n/a	negative	n/a	n/a

180 patients with GRF (glomerular filtration rate) calculated at 19 ± 6 mL/min/m^2.

The percent variation (Δ%) and mean changes (mg/dL ± SD) in plasma lipid and lipoprotein profile and GFR, at baseline (T0), after 6 (T6), 12 (T12), 18 (T8) and 24 (T24) months treatment with Diflstat®

HDLC: high density lipoprotein-cholesterol; LDLC: low-density lipoprotein-cholesterol; TC: total cholesterol; non-HDLC: non high density lipoprotein-cholesterol; TG: triglycerides; n.s. = not significant; n/a = not applicable; *P* value ≤ 0.001.

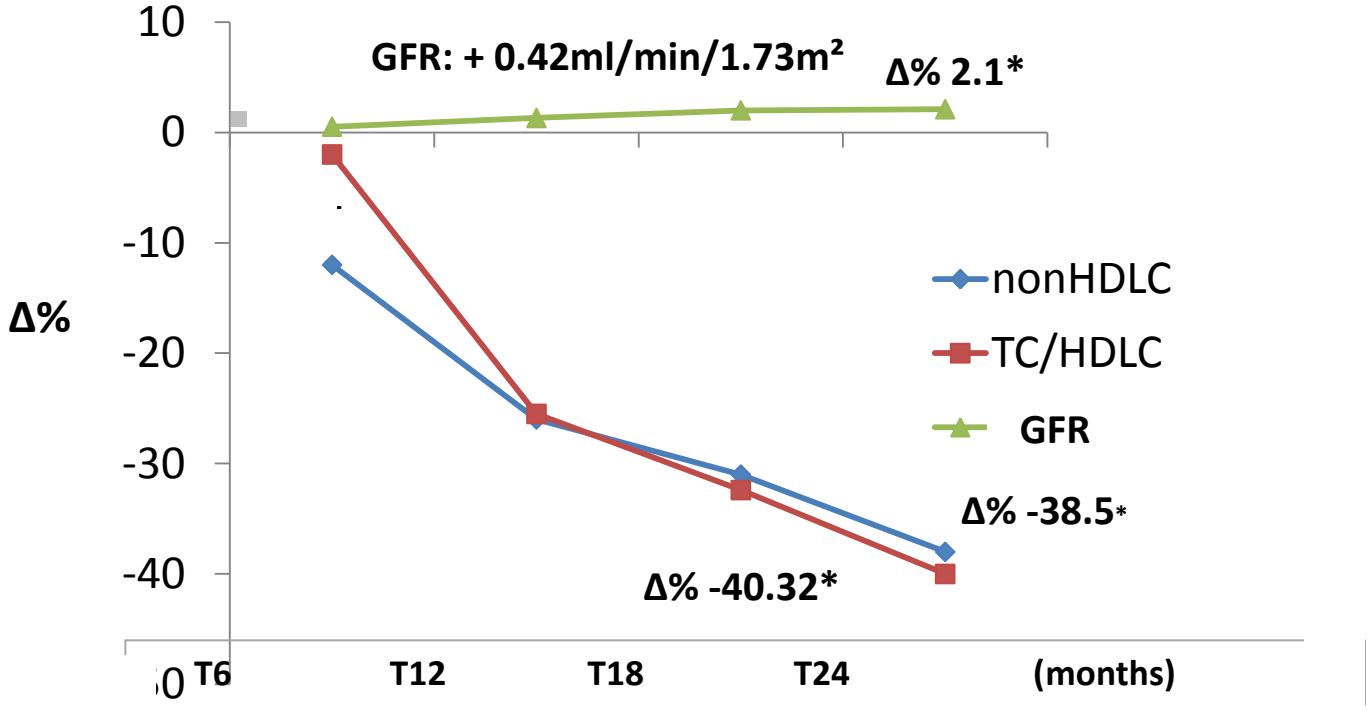
Group C

Stage IV of CKD according to KDOQI classification.

180 patients with glomerular filtration rate (GFR) calculated at 19 ± 6 mL/min/1.73m.²

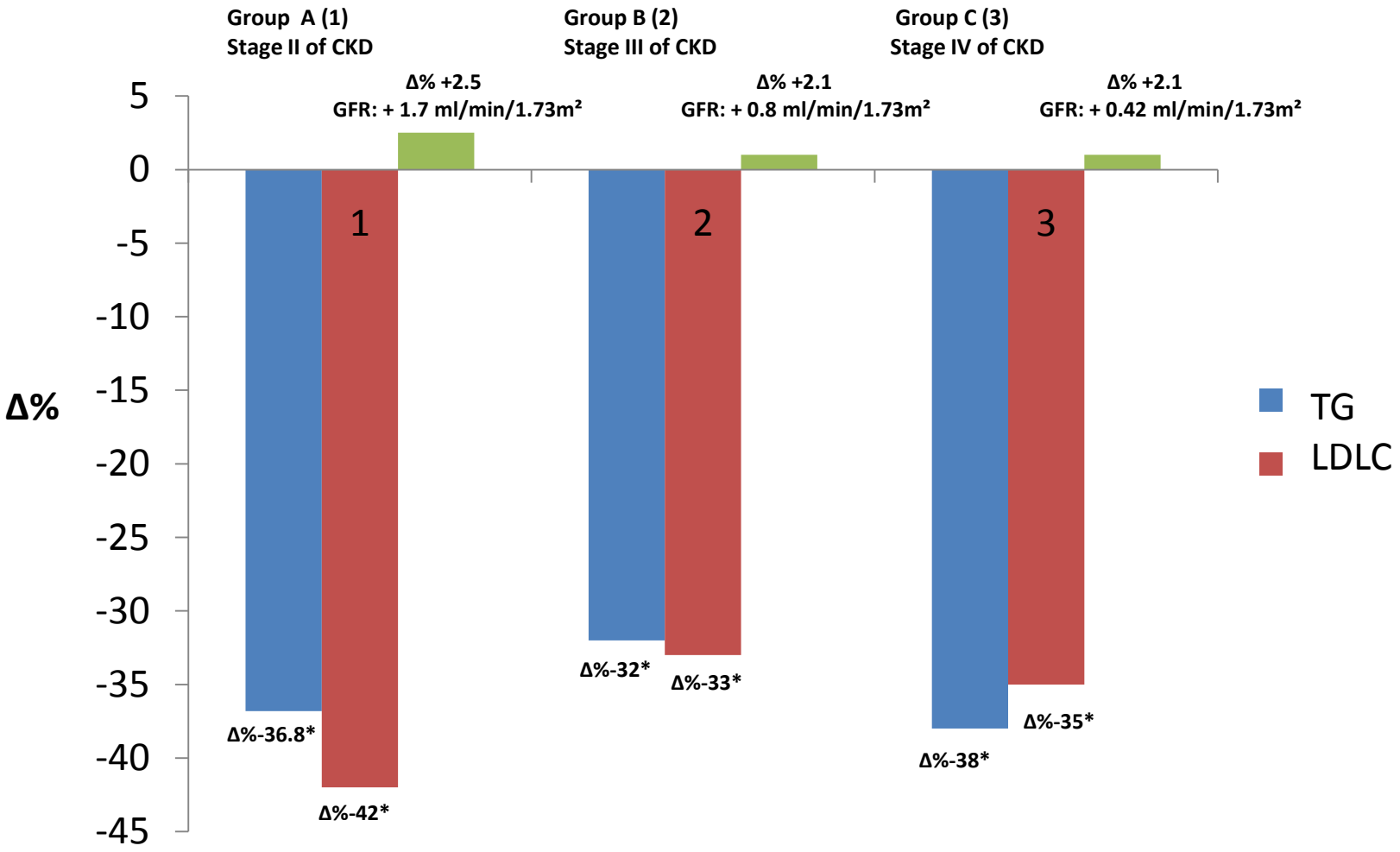
The percent variation (Δ%) of plasma non- high density lipoprotein cholesterol (non-HDLC) and TC/HDLC in patients with secondary dyslipidemia, at baseline (T0), after 6 (T6), 12 (T12), 18 (T8) and 24 (T24) months treatment with Dif1stat ®

*** P ≤ 0.001**



The percent variation (Δ%) of plasma triglycerides (TG), low-density lipoprotein-cholesterol (LDLC), in patients with secondary dyslipidemia, after 24 months treatment with Dif1stat ®

* P ≤ 0.001



Conclusion

- To all patients considered for this study, a non-pharmaceutical, nutraceutical treatment was prescribed which, paired with a special diet, contributed to an improved plasma lipid and lipoprotein pattern
- No patient showed at the end of the study a worsening of kidney function as expressed by GFR level, compared with those values displayed at the onset of treatment or the appearance of albuminuria.
- The sooner the lipid-lowering treatment is begun, without modifying nutraceutic dose, on patients with CKD, the better the results are on the lipid and lipoprotein profile.

Thank you for your attention !