

## *Supplementary Material*

### **Remnant Cholesterol Is Independently Associated with an Increased Risk of Peripheral Artery Disease in Type 2 Diabetic Patients**

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The severity of PAD was assessed using the Fontaine classification, comprising four stages: I - asymptomatic; II - intermittent claudication; III - rest pain; and IV - ischemic ulcers or gangrene (27).

We separated T2DM-PAD and T2DM-WPAD patients based on whether or not they were taking statins to determine whether statin use affected the RC levels. As shown in the Supplementary Table 1 and Table 2, there were no significant differences between the statin and non-statin subgroups in terms of RC. Comparing the PAD and WPAD groups of patients with LDL-C at target levels, a significant difference in RC levels was found. Elevated RC levels might explain the increased risk of PAD in DM patients with LDL-C at target. (See Supplementary Table 3)

Based on the Fontaine classification, we evaluated the degree of PAD disease and then categorized the patients with T2DM - PAD into three subgroups: Fontaine stage II, III, and IV. There was no significant correlation between RC and disease severity in any of the three patient groups.

#### **Supplementary Table 1. Baseline and laboratory findings of T2DM-WPAD patients with statins or without statins**

Variables	Non-statins (N=217)	Statins (N=29)	<i>P</i> value
Gender (male, %)	121(55.8%)	14(48.3%)	0.447
Age (years)	56±9	57±10	0.153
Diabetes duration (years)	4(1-10)	5(2-10)	0.281
Smoking, n (%)	64(29.5%)	5(17.2%)	0.168

Alcohol, n (%)	54(24.9%)	6(20.7%)	0.621
Hypertension, n (%)	<b>98(45.2%)</b>	<b>22(75.9%)</b>	<b>0.002</b>
Dyslipidemia, n (%)	<b>73(33.6%)</b>	<b>17(58.6%)</b>	<b>0.009</b>
SBP (mmHg)	128(117-140)	122(116-135)	0.153
DBP (mmHg)	<b>80(72-87)</b>	<b>77(68-82)</b>	<b>0.016</b>
ALT, U/L	20.3(14.8-31.2)	20.9(14.3-26)	0.511
AST, U/L	20(16-25.3)	22.1(16.1-27.4)	0.565
Urea, mmol/L	5.54(4.48-6.36)	5.3(4.93-6.43)	0.395
Cr, UMOL/L	63.3(52.4-77.4)	56.8(46.1-74.4)	0.262
eGFR(ml/min/1.73m <sup>2</sup> )	102.5(91.4-112.1)	99.7(91-106.7)	0.441
Uric Acid, μmol/L	310.2±87.1	303±86.8	0.853
CRP, mg/L	1.2(0.7-2.4)	1.4(0.8-2.3)	0.939
FPG, mmol/L	<b>10.56(7.55-14.95)</b>	<b>7.97(6.19-13.61)</b>	<b>0.015</b>
HbA1c (%)	8.3(6.8-10)	7.3(6.5-8.9)	0.112
TG, mmol/L	1.54(1.08-2.21)	1.6(1.08-2.2)	0.894
TC, mmol/L	<b>4.62±1.06</b>	<b>3.82±0.93</b>	<b>&lt;0.001</b>
HDL-C, mmol/L	1.12(0.97-1.38)	1.15(0.93-1.37)	0.836
LDL-C, mmol/L	<b>2.97±0.98</b>	<b>2.01±0.72</b>	<b>&lt;0.001</b>
N-HDL-C, mmol/L	<b>3.52(2.88-4.15)</b>	<b>2.54(2.25-3.17)</b>	<b>&lt;0.001</b>
RC, mmol/L	0.55(0.37-0.7)	0.57(0.52-0.87)	0.076
TyG index	7.89(7.27-8.48)	7.55(7.16-8.45)	0.169
Neutrophil, 10 <sup>9</sup> /L	3.43(2.82-4.46)	3.39(3.01-4.27)	0.900
Lymphocyte, 10 <sup>9</sup> /L	1.7(1.42-2.05)	1.65(1.38-1.88)	0.432
Monocyte, 10 <sup>9</sup> /L	0.34(0.28-0.42)	0.37(0.27-0.4)	0.885
Platelet, 10 <sup>9</sup> /L	207(176-242)	206(189-248)	0.708
NLR	2.05(1.59-2.53)	2.02(1.78-2.72)	0.672
MLR	0.19(0.16-0.25)	0.21(0.17-0.27)	0.391
PHR	176.53(143.06-237.76)	184.21(142.68-235.79)	0.649
Use antidiabetes agents			
Insulin, n (%)	26(12%)	1(3.4%)	0.198
Oral drugs, n (%)	100(46%)	11(37.9%)	
Diet control only, n (%)	62(28.6%)	10(34.5%)	
Insulin + Drugs, n (%)	29(13.4%)	7(24%)	

SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, creatinine; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; N-HDL-C, non-HDL-C; RC, remnant cholesterol; TyG index, triglyceride glucose index; NLR, neutrophil to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; PHR, platelet/HDL-C ratio.  $P < 0.05$  (two-sided) was defined as statistically significant. Bold values indicate statistical significance.

**Supplementary Table2. Baseline and laboratory findings of T2DM-PAD patients with statins or without statins**

Variables	Non-statins (N=215)	Statins (N=55)	P value
Gender (male, %)	128(59.5%)	28(50.9%)	0.248
Age (years)	65(59-71)	66(61-69.5)	0.756
Diabetes duration (years)	10(5-18)	10(5-18.5)	0.922
Smoking, n (%)	61(28.4%)	12(21.8%)	0.329
Alcohol, n (%)	57(26.5%)	11(20%)	0.321
Hypertension, n (%)	<b>126(58.6%)</b>	<b>41(74.5%)</b>	<b>0.030</b>
Dyslipidemia, n (%)	<b>67(31.2%)</b>	<b>25(45.5%)</b>	<b>0.046</b>
SBP (mmHg)	133(123-144.5)	130(122-142.5)	0.392
DBP (mmHg)	78(70-85)	76(70-81)	0.143
ALT, U/L	16.6(11.6-22.15)	19.1(14.6-27.25)	0.093
AST, U/L	18(15.65-24.2)	20.7(16.95-25.95)	0.087
Urea, mmol/L	5.93(4.51-7.22)	5.83(4.86-7.15)	0.718
Cr, UMOL/L	70.2(56.3-86)	71.1(59.7-78.3)	0.965
eGFR(ml/min/1.73m <sup>2</sup> )	90.9(72.35-104.2)	92.8(71.2-101.3)	0.941
Uric Acid, μmol/L	316.3(243.95-380.2)	324.6(275-372.65)	0.670
CRP, mg/L	2.2(1.1-6.15)	1.9(1-4.5)	0.255
FPG, mmol/L	10.1(8-15.1)	9.59(6.59-13.64)	0.131
HbA1c (%)	8.3(7.2-9.95)	8.1(7.1-9.3)	0.490
TG, mmol/L	1.66(1.14-2.36)	1.66(1.135-2.505)	0.886
TC, mmol/L	<b>4.68(3.84-5.52)</b>	<b>3.82(3.39-4.63)</b>	<b>&lt;0.001</b>
HDL-C, mmol/L	1(0.86-1.16)	1(0.865-1.15)	0.964
LDL-C, mmol/L	<b>2.72(2.1-3.49)</b>	<b>1.98(1.69-2.47)</b>	<b>&lt;0.001</b>
N-HDL-C, mmol/L	<b>3.58(2.8-4.4)</b>	<b>2.73(2.26-3.55)</b>	<b>&lt;0.001</b>
RC, mmol/L	0.76(0.61-1.05)	0.75(0.56-0.99)	0.487
TyG index	7.96(7.38-8.5)	7.85(7.175-8.35)	0.296
Neutrophil, 10 <sup>9</sup> /L	3.99(3.09-5.13)	3.91(3.32-5.04)	0.895
Lymphocyte, 10 <sup>9</sup> /L	1.44(1.12-1.81)	1.58(1.26-1.88)	0.154
Monocyte, 10 <sup>9</sup> /L	0.38(0.3-0.49)	0.4(0.3-0.52)	0.643
Platelet, 10 <sup>9</sup> /L	212(172-260)	195(169-243)	0.275
NLR	2.66(1.96-3.75)	2.55(1.785-3.56)	0.311
MLR	0.26(0.19-0.36)	0.24(0.19-0.33)	0.497
PHR	204.11(163.25-276.29)	201(152.75-271.76)	0.746
Use antidiabetes agents			
Insulin, n (%)	51(23.7%) a	8(14.5%) a	
Oral drugs, n (%)	98(45.6%) a	18(32.7%) a	

Diet control only, n (%)	18(8.4%) a	5(9.1%) a	
Insulin + Drugs, n (%)	<b>48(22.3%) a</b>	<b>24(43.6%) b</b>	<b>0.013</b>
PAD			
Mild PAD, n (%)	108(50.2%)	29(52.7%)	0.806
Moderate PAD, n (%)	52(24.2%)	11(20.0%)	
Severe PAD, n (%)	55(25.6%)	15(27.3%)	

SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, creatinine; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; N-HDL-C, non-HDL-C; RC, remnant cholesterol; TyG index, triglyceride glucose index; NLR, neutrophil to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; PHR, platelet/HDL-C ratio.  $P < 0.05$  (two-sided) was defined as statistically significant. Bold values indicate statistical significance. a, b: after applying the chi-square test, different superscripts indicate statistically different categorical variables between the 2 groups.

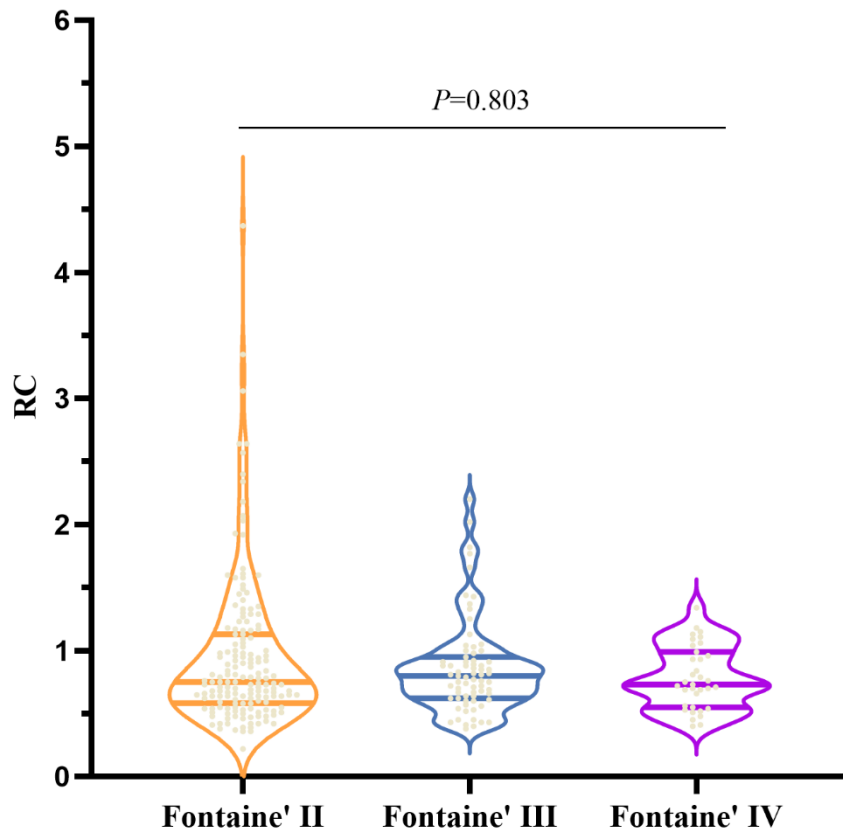
**Supplementary Table 3. Demographic and clinical data of WPAD and PAD patients with LDL level < 1.8 mmol/L**

Variables	WPAD (N=38)	PAD (N=57)	P value
Gender (male, %)	24(63.2%)	37(64.9%)	0.861
Age (years)	<b>57.5(52-64)</b>	<b>65(59-71)</b>	<b>&lt;0.001</b>
Diabetes duration (years)	<b>6.5(2-10)</b>	<b>14(4-20)</b>	<b>0.002</b>
Smoking, n (%)	11(28.9%)	13(22.8%)	0.500
Alcohol, n (%)	13(34.2%)	14(24.6%)	0.307
Hypertension, n (%)	22(57.9%)	37(64.9%)	0.490
Dyslipidemia, n (%)	11(28.9%)	15(26.3%)	0.778
Statins	9(23.7%)	19(33.3%)	0.312
SBP (mmHg)	127(119-142)	132(122-140)	0.494
DBP (mmHg)	79(72-85)	78(72-82)	0.270
ALT, U/L	21.15(14-30.9)	19.1(13.1-29.4)	0.310
AST, U/L	20.1(16.7-25.5)	18.8(16-26.9)	0.679
Urea, mmol/L	5.955(4.86-7.6)	6.04(4.53-7.57)	0.939
Cr, UMOL/L	<b>67.75(49.9-83.7)</b>	<b>76.9(65.5-91.2)</b>	<b>0.013</b>
eGFR(ml/min/1.73m <sup>2</sup> )	<b>98.35(91-106.7)</b>	<b>86.1(68.5-99.4)</b>	<b>0.005</b>
Uric Acid, μmol/L	305.7(246.9-377.2)	334.3(287.2-373.9)	0.085
CRP, mg/L	1.4(0.6-2.7)	2(1-6.3)	0.063
FPG, mmol/L	10.615(6.56-15)	8.46(6.36-12.16)	0.277
HbA1c (%)	7.45(6.7-8.9)	7.6(6.7-9.1)	0.779
TG, mmol/L	1.155(0.71-2.19)	1.21(0.82-1.81)	0.979
TC, mmol/L	3.12(2.75-3.52)	3.21(2.95-3.37)	0.403

HDL-C, mmol/L	<b>1.02(0.8-1.34)</b>	<b>0.9(0.73-1.06)</b>	<b>0.028</b>
LDL-C, mmol/L	<b>1.43(1.26-1.57)</b>	<b>1.56(1.36-1.67)</b>	<b>0.030</b>
N-HDL-C, mmol/L	<b>2.08(1.78-2.31)</b>	<b>2.24(2.05-2.44)</b>	<b>0.037</b>
RC, mmol/L	<b>0.51(0.42-0.7)</b>	<b>0.73(0.55-0.9)</b>	<b>0.002</b>
TyG index	7.64(6.97-8.16)	7.34(7.07-8.31)	0.514
Neutrophil ,10 <sup>9</sup> /L	3.94(2.77-4.67)	4.07(3.02-5.22)	0.511
Lymphocyte, 10 <sup>9</sup> /L	<b>1.76(1.37-1.91)</b>	<b>1.36(1.05-1.73)</b>	<b>0.015</b>
Monocyte, 10 <sup>9</sup> /L	0.375(0.29-0.46)	0.41(0.29-0.54)	0.185
Platelet, 10 <sup>9</sup> /L	203(177-231)	195(160-258)	0.802
NLR	<b>2.17(1.52-3.12)</b>	<b>2.75(1.86-3.78)</b>	<b>0.043</b>
MLR	<b>0.2(0.16-0.28)</b>	<b>0.27(0.21-0.38)</b>	<b>0.005</b>
PHR	186.39(154.55-265.52)	226.85(170-310.71)	0.117
Use antidiabetes agents			
Insulin, n (%)	9(23.7%)	22(38.6%)	0.096
Oral drugs, n (%)	12(31.6%)	13(22.8%)	
Diet control only, n (%)	7(18.4%)	3(5.3%)	
Insulin + Drugs, n (%)	10(26.3%)	19(33.3%)	
PAD			
Mild PAD, n (%)	/	27(47.4%)	/
Moderate PAD, n (%)	/	14(24.6%)	/
Severe PAD, n (%)	/	16(28.1%)	/

SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, creatinine; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; N-HDL-C, non-HDL-C; RC, remnant cholesterol; TyG index, triglyceride glucose index; NLR, neutrophil to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; PHR, platelet/HDL-C ratio.  $P < 0.05$  (two-sided) was defined as statistically significant. Bold values indicate statistical significance.

**Supplementary Figure1. RC level according to PAD severity based on the Fontaine classification.**



RC, remnant cholesterol. In the violin plot, the three horizontal lines from top to bottom represent the upper quartile, the median, and the lower quartile in order.  $P < 0.05$  (two-sided) was defined as statistically significant. Bold values indicate statistical significance.