·临床研究·

沙库巴曲缬沙坦对慢性射血分数降低心力衰竭合并肾功能不全患者的肾脏保护作用

贾红丹,毕希乐,赵云凤,宋婷婷,刘丽*
(秦皇岛市第一医院心血管内科,河北 秦皇岛 066000)

【摘 要】 **目的** 观察沙库巴曲缬沙坦对合并肾功能不全的慢性心力衰竭(简称心衰)患者肾功能的影响。**方法** 连续纳入2020年12月至2022年3月秦皇岛市第一医院慢性心衰合并肾功能不全患者84例,分为沙库巴曲缬沙坦组(n=48)和对照组(n=36)。沙库巴曲缬沙坦组接受沙库巴曲缬沙坦治疗,对照组接受单一的缬沙坦治疗。观察2组患者服药后6个月和12个月肌酐、估算的肾小球滤过率(eGFR)、尿素氮、尿酸、肾功能恶化(WRF)指标的变化情况。采用SPSS 22.0软件进行数据分析。根据数据类型,组间比较分别采用t检验、非参数秩和检验、非参数检验、Mann-Whitney U检验及χ^2检验。**结果** 服药后6个月,对比基线水平,沙库巴曲缬沙坦组肌酐、eGFR的变化值与对照组比较无明显差异;尿素氮及尿酸下降值显著高于对照组[-2.62(1.83,3.90)和0.45(0.29,0.70) mmol/L, P<0.01;-137.00(-92.30,-201.13)和-9.65(49.00,-79.80) μmol/L, P=0.000];与对照组比较,沙库巴曲缬沙坦降低了患者的收缩压及舒张压[(132±17)和(133±24) mmHg(1 mmHg=0.133 kPa), P=0.824;(81±14)和(82±12) mmHg, P=0.732],但尚无统计学差异,NYHA分级明显改善(Z=-2.150, P=0.032)。服药后12个月,对比基线水平,沙库巴曲缬沙坦组eGFR下降值明显低于对照组[-2.21(1.33,3.49)和-22.11(12.32,29.67) ml/(min·1.73m^2), P=0.023];肌酐升高值明显低于对照组[1.50(0.98,2.07)和31.65(22.77,42.53) μmol/L, P=0.043];尿素氮及尿酸下降值也显著高于对照组[-2.80(2.01,4.23)和0.80(0.58,1.14) mmol/L, P<0.01;-141.00(-96.40,-200.25)和-8.45(45.00,-77.70) μmol/L, P=0.000];沙库巴曲缬沙坦组收缩压及舒张压降幅、NYHA分级均显著优于对照组[(123±14)和(130±17) mmHg, P=0.042;(76±11)和(81±11) mmHg, P=0.042; Z=-2.200, P=0.028]。服药后6个月,沙库巴曲缬沙坦组WRF发生率与对照组相比无明显统计学差异[3(6.25%)和7(19.44%), P=0.132];服药后12个月,沙库巴曲缬沙坦组WRF发生率显著低于对照组[4(8.33%)和9(25.00%), P=0.037]。**结论** 沙库巴曲缬沙坦组心功能改善先于肾脏保护出现,血压降低和肾脏保护同步。与单一的缬沙坦比较,沙库巴曲缬沙坦可以延缓、控制合并肾功能不全的慢性心衰患者肾功能的恶化,减少WRF的发生。随服药时间的延长,对肾功能的保护作用更显著。

【关键词】 慢性心力衰竭;肾功能不全;沙库巴曲缬沙坦;肾功能恶化
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Renal protective effect of sacubitril/valsartan in and renal insufficiency patients with chronic heart failure with reduced ejection fraction

Jia Hongdan, Bi Xile, Zhao Yunfeng, Song Tingting, Liu Li*
(Department of Cardiology, First Hospital of Qinhuangdao, Qinhuangdao 066000, Hebei Province, China)

【**Abstract**】 **Objective** To observe the effect of sacubitril/valsartan on renal function in patients with chronic heart failure (CHF) and renal insufficiency. **Methods** A total of 84 consecutive CHF patients with renal insufficiency who visited the First Hospital of Qinhuangdao form December 2020 to March 2022 were enrolled and divided into sacubitril/valsartan group (n=48) and control group (n=36). The sacubitril/valsartan group received sacubitril/valsartan and the control group received single valsartan. The two groups were observed for the changes in serum creatinine, estimated glomerular filtration rate (eGFR), urea nitrogen, uric acid, and worsening renal function (WRF) at 6 and 12 months after medication. SPSS statistics 22.0 was used for statistical analysis. Data comparison between two groups was perfomed using t test, non-parametric rank sum test, non-parametric test, Mann-Whitney U test or χ^2 test depending on data type. **Results** At 6 months, there were no significant differences in serum creatinine (P=0.254) and eGFR (P=0.061) in comparison with the baseline between the two groups. The decreased values of urea nitrogen [-2.62 (1.83,3.90) *vs* 0.45 (0.29,0.70) mmol/L; P<0.01] and uric acid [-137.00(-92.30,-201.13) *vs* -9.65(49.00,-79.80) μmol/L; P=0.000] were significantly higher in the

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通信作者: 刘丽, E-mail: lucy301bj@sina.com

sacubitril/valsartan group than those in the control group. Compared with the control group, sacubitril/valsartan reduced systolic blood pressure [(132±17) *vs* (133±24) mmHg (1 mmHg=0.133 kPa); *P*=0.824] and diastolic blood pressure [(81±14) *vs* (82±12) mmHg; *P*=0.732], but there was no statistical differences. NYHA classification was significantly improved between two groups (*Z*=-2.150; *P*=0.032). Compared with the baseline at, 12 months, the decline of eGFR was lower in the sacubitril/valsartan group than the control group [-2.21 (1.33,3.49) *vs* -22.11 (12.32,29.67) ml/(min·1.73 m^2); *P*=0.023]; the increase in serum creatinine was significantly lower in the sacubitril/valsartan group than in the control group [1.50 (0.98,2.07) *vs* 31.65 (22.77,42.53) μmol/L; *P*=0.043]; the decreases in urea nitrogen [-2.80 (2.01,4.23) *vs* 0.80 (0.58,1.14) mmol/L; *P*<0.01] and uric acid [-141.00(-96.40,-200.25) *vs* -8.45(45.00,-77.70) μmol/L; *P*=0.011] were significantly higher in the the sacubitril/valsartan group than in the control group. The sacubitril/valsartan group had a significantly greater reduction in systolic blood pressure [(123±14) *vs* (130±17) mmHg; *P*=0.042] and diastolic blood pressure [(76±11) *vs* (81±11) mmHg; *P*=0.042] and significantly better NYHA classification (*Z*=-2.200; *P*=0.028) than the control group. There was no significant difference in the incidence of WRF [3 (6.25%) *vs* 7 (19.44%); *P*=0.132] between the two groups at 6 months, but at 12 months, the incidence of WRF in the sacubitril/valsartan group is significantly lower than that in the control group [4 (8.33%) *vs* 9 (25.00%); *P*=0.037]. **Conclusion** In the sacubitril/valsartan group, improvement in cardiac function precedes the effect of renal protection, and blood pressure decreases simultaneously with effect of renal protection. Compared with single valsartan, sacubitril/valsartan can delay and control the worsening of renal function in CHF patients with renal insufficiency and reduce the occurrence of WRF. The renal protective effect of sacubitril/valsartan is more significant with the prolongation of medication.

【Key words】 chronic heart failure; renal insufficiency; Sacubitril/Valsartan; worsening renal function

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Corresponding author: *Liu Li*, *E-mail*: *lucy301bj@sina.com*

慢性心力衰竭(简称心衰)患者心脏泵功能衰竭导致肾脏低灌注、氧化应激、炎症、纤维化等,肾功能不全的发生率高[1]。具有同时抑制脑啡肽酶和血管紧张素Ⅱ受体作用的沙库巴曲缬沙坦是一种新型的盐复合物晶体药物,PARADIGM-HF 慢性肾脏病亚组分析显示[2],沙库巴曲缬沙坦可降低估算的肾小球滤过率(estimated glomerular filtration rate, eGFR),改善慢性肾脏病患者的心血管结局,但对射血分数降低心力衰竭(heart failure with reduced ejection fraction, HFrEF)合并肾功能不全患者肾功能的影响,目前研究报道还很少。欧洲心脏病学会心力衰竭协会指出,与 eGFR 等肾功能评估指标相比,肾功能恶化(worsening renal function, WRF)是评估肾功能的动态指标,它受肾脏血流灌注、肾脏病变进展和药物相关因素等多种因素影响,能够更全面地反应疾病或药物对肾功能的影响。本研究旨在评估沙库巴曲缬沙坦对合并肾功能不全的心衰患者肾功能的保护作用。

1 对象与方法

1.1 研究对象

连续纳入 2020 年 12 月至 2022 年 3 月于秦皇岛市第一医院就诊的慢性心衰合并肾功能不全患者 84 例,其中男性 63 例,女性 21 例,年龄 31~81(63.68±13.32)岁。其中扩张型心肌病 45 例(53.57%),缺血性心肌病 36 例(42.86%),其他类型心衰(心肌致密化不全、心动过速性心肌病)3 例(3.57%)。纳入标准:(1)年龄≥18 岁,依据 2021 欧洲心脏病学会指南[3],存在心衰的症状和(或)体征以及心功能不全的客观证据,确诊为慢性心衰≥3 个月;(2)美国纽约心脏联合会(New York Heart Association, NYHA)分级Ⅱ~Ⅲ级,左室射血分数(left ventricular ejection fraction, LVEF)≤40%;(3)临床情况相对稳定的住院患者和门诊患者均接受标准化的抗心衰治疗;(4)合并肾功能不全,慢性肾功能不全诊断及分期依据改善全球肾脏病预后组织指南[eGFR<90 ml/(min·1.73m^2)][4]。排除标准:(1)当前患有急性失代偿性心衰;(2)低血压,收缩压≤95 mmHg(1 mmHg=0.133 kPa);(3)既往出现血管性水肿;(4)eGFR<15 ml/(min·1.73m^2);(5)血清钾≥5.2 mmol/L;(6)重度肝功能损害。本研究符合秦皇岛市第一医院伦理委员会制定的伦理标准,所有患者均签署知情同意书。

1.2 方法

1.2.1 分组 按照随机数字表法随机将 84 例入选患者分为 2 组。沙库巴曲缬沙坦组患者 48 例,其中男性 39 例,女性 9 例,年龄 31~80(61.44±14.77)岁;对照组患者 36 例,其中男性 24 例,女性 12 例,年龄 46~81(66.67±10.58)岁。首次接诊收集患者的一般资料及病史,完成 NYHA 分级,对患者血浆生化、血浆 B 型脑钠肽(brain natriuretic peptide, BNP)等进行检测。由超声科同一位医师完成心脏超声及心功能检查,将首次接诊时的一般情况和检测指标作为基线指标。

1.2.2 干预方案 2 组均给予 β 受体阻滞剂、醛固酮受体拮抗剂螺内酯、呋塞米等标准化抗心衰治疗(药物禁忌证除外)。对照组患者给予缬沙坦,依据

血压将缬沙坦逐渐滴定至靶剂量(160 mg、2 次/d)或最大耐受剂量;沙库巴曲缬沙坦组给予沙库巴曲缬沙坦,25 mg、2 次/d 为起始剂量,依据血压逐渐滴定至靶剂量 200 mg、2 次/d,或患者最大耐受剂量,使患者血压不低于 90/60 mmHg。随访时间为服药后 6 个月和 12 个月,采用门诊随访形式。

1.2.3 肾功能评价指标 服药至研究预定终点时,对 2 组患者进行如下检测:晨时空腹 8 h 以上肘静脉血测定肌酐、尿素氮、尿酸,并根据患者的性别、年龄、体质量和肌酐,按照 Cockcroft-Gault 公式,计算出患者的内生肌酐清除率代替 eGFR。WRF[5] 由肌酐的变化来评价,定义为肌酐升高 > 0.3 mg/dl (26.52 μmol/L)或两个时间点间肌酐升高 25%以上。

1.3 统计学处理

采用 SPSS 22.0 统计软件进行数据分析。符合正态分布的计量资料用均数±标准差($\bar{x}\pm s$)表示,采用 t 检验;非正态分布的计量资料用中位数(四分位数间距)[$M(Q_1, Q_3)$]表示,采用非参数秩和检验;组内治疗前后不同时间点的肾功能指标对比采用多个相关样本的非参数检验;等级资料采用 Mann-Whitney U 秩和检验。计数资料用例数(百分率)表示,采用 χ^2 检验。$P<0.05$ 为差异有统计学意义。

2 结 果

2.1 2 组患者临床基线资料比较

2 组患者的性别、年龄、病史、血压、尿量、肾功能、心脏结构功能、呋塞米应用剂量、用药情况等方面比较,差异均无统计学意义(均 $P>0.05$)。其中肌酐>221 μmol/L 患者 6 例(7.14%;表 1)。

表 1 2 组患者临床基线资料比较

Table 1 Comparison of clinical data between two groups

Variable	Sacubitril/Valsartan group(n=48)	Control group (n=36)	P value
Gender(male/female, n)	39/9	24/12	0.127
Age(years, $\bar{x}\pm s$)	61.44±14.77	66.67±10.58	0.075
Hypertension[n(%)]	16(33.33)	13(36.11)	0.791
SBP(mmHg, $\bar{x}\pm s$)	149±22	145±30	0.483
DBP(mmHg, $\bar{x}\pm s$)	90±13	88±13	0.487
Diabetes mellitus[n(%)]	14(29.17)	10(27.78)	0.889
24-hour urine volume(ml, $\bar{x}\pm s$)	890.63±121.45	870.83±138.04	0.488
Creatinine[μmol/L, $M(Q_1, Q_3)$]	101.00(81.15,126.86)	89.75(66.56,101.19)	0.061
eGFR[ml/(min · 1.73m^2), $M(Q_1, Q_3)$]	64.41(50.51,82.03)	75.39(60.63,87.32)	0.073
BUN[mmol/L, $M(Q_1, Q_3)$]	8.04(5.97,16.95)	8.70(6.12,10.37)	0.417
Serum uric acid[μmol/L, $M(Q_1, Q_3)$]	481.50(374.65,581.75)	495.70(381.80,622.35)	0.543
BNP[pg/ml, $M(Q_1, Q_3)$]	1600(590,4090)	2057(955,3058)	0.114
NT-proBNP[pg/ml, $M(Q_1, Q_3)$]	5346(1963,13538)	6911(3065,11971)	0.123
LVDD(mm, $\bar{x}\pm s$)	69.03±12.11	69.06±6.91	0.990
Cardiac output(L/min, $\bar{x}\pm s$)	5.66±2.49	6.04±1.66	0.466
LVEF(%, $\bar{x}\pm s$)	27.26±6.24	30.46±9.55	0.068
NYHA class[n(%)]			
Ⅱ	15(31.25)	12(33.33)	0.840
Ⅲ	33(68.75)	24(66.67)	0.840
Dose of furosemide(mg, $\bar{x}\pm s$)	23.75±7.89	20.86±5.26	0.063
Beta blocker[n(%)]	32(66.7)	22(61.1)	0.520
ACEI/ARB[n(%)]	26(54.2)	20(55.6)	0.957
Aldosterone antagonist[n(%)]	40(83.3)	28(77.8)	0.159
Statins[n(%)]	39(81.3)	32(88.9)	0.186
Aspirin/Clopidogrel[n(%)]	33(68.8)	25(69.4)	0.955
Anticoagulant[n(%)]	9(18.8)	6(16.7)	0.737
Nitrates[n(%)]	30(62.5)	18(50.0)	0.052
Calcium channel blocker[n(%)]	7(14.6)	8(22.2)	0.113
SGLT-2i[n(%)]	17(35.4)	12(33.3)	0.622

SBP: systolic blood pressure; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; BUN: blood urea nitrogen; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-B-type natriuretic peptide; LVDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; ACEI/ARB: angiotensin converting enzyme inhibitor/angiotensin Ⅱ receptor blocker; SGLT-2i: sodium-glucose cotransporter 2 inhibitor. 1 mmHg=0.133 kPa.

2.2 2组患者服药后6个月及12个月临床效果比较

2组患者服药后6个月,对比基线水平,肌酐、eGFR的变化量无显著性差异($P=0.254$,0.061);尿素氮及尿酸的变化量,差异有统计学意义($P=0.000$,0.000;表2)。与对照组相比,沙库巴曲缬沙坦组患者的收缩压及舒张压均降低,但差异无统计学意义[(132±17)和(133±24)mmHg,(81±14)和(82±12)mmHg;均$P>0.05$];NYHA分级明显改善($Z=-2.150$,$P=0.032$)。

2组患者服药后12个月,对比基线水平,沙库巴曲缬沙坦组eGFR下降幅度及肌酐升高幅度较对照组小($P<0.05$);2组尿素氮及尿酸的变化量仍有显著性差异($P<0.05$;表2)。沙库巴曲缬沙坦组收缩压及舒张压均低于对照组[(123±14)和(130±17)mmHg,(76±11)和(81±11)mmHg;均$P<0.05$],NYHA分级均显著优于对照组($Z=-2.200$,$P=0.028$)。

2.3 2组患者服药后6个月及12个月WRF的比较

随访6个月时,沙库巴曲缬沙坦组和对照组WRF发生率比较,差异无统计学意义[3(6.25%)和7(19.44%),$P=0.132$];随访12个月时,沙库巴曲缬沙坦组WRF发生率低于缬沙坦组,差异有统计学意义[4(8.33%)和9(25.00%),$P=0.037$]。

3 讨 论

慢性心衰患者大多存在心肾共病现象,并交互影响[6]。COACH研究[7]纳入了1 023例心衰住院患者,随访入院、出院及出院后6个月和12个月的eGFR和WRF的发生率,结果显示11%的患者住院期间发生WRF,而16%和9%的患者分别在出院后0~6个月和6~12个月发生了WRF,在心衰的治疗过程中如何进一步兼顾肾功能,甚至延缓、控制肾功能的进行性恶化是临床上亟待解决的问题。研究表明肾素-血管紧张素-醛固酮系统(renin-angiotensin-aldosterone system,RAAS)及交感神经系统的过度活跃、血流动力学的紊乱、炎症反应及氧化应激是心脏疾病发展加重的主要病理生理学基础[1,8],RAAS抑制剂治疗心衰通常伴有血清肌酐的升高[9],本研究旨在比较沙库巴曲缬沙坦与缬沙坦对合并肾功能不全的HFrEF患者肾功能进展变化的影响。

本研究对2组HFrEF合并肾功能不全患者分别给予缬沙坦和沙库巴曲缬沙坦治疗,结果显示,虽然服药后6个月和12个月的eGFR均有所下降,但服药12个月时,沙库巴曲缬沙坦组患者eGFR下降幅度较对照组较小,差异有统计学意义,说明沙库巴曲缬沙坦较缬沙坦延缓肾功能进展的作用更强,将WRF出现的时间推迟,这与国外研究结果一致[7,10]。血尿酸水平的升高是肾功能下降的独立危险因素,是不良预后的独立预测因子[11],降低血尿酸水平可减少氧化应激及RAAS激活,从而对肾脏产生保护作用,甚至逆转肾功能的下降[12]。本研究结果表明,沙库巴曲缬沙坦组患者尿酸的下降情况在6个月及12个月时均优于对照组,初期下降幅度较大,后期下降幅度减少,这与PARADIGM-HF尿酸亚组分析结果一致,提示沙库巴曲缬沙坦可降低血尿酸浓度。沙库巴曲缬沙坦对尿酸的作用机制目前尚不清楚,在一项小规模的人类志愿者研究中,脑啡肽酶抑制剂可以增加尿酸排泄,这与一种双重作用的脑啡肽酶-血管紧张素转换酶抑制剂的作用机制类似。血尿酸水平本身也能反应氧化应激,它可以增加细胞因子和趋化因子的表达,但沙库巴曲缬沙坦对血尿酸的影响是否伴随炎症标志物的变化目前研究尚未评估。

表2 2组患者服药前后肾功能比较

Table 2 Comparison of renal function before and after medication between two groups [$M(Q_1, Q_3)$]

Renal function index	Medication duration	Difference with before treatment in Sacubitril/Valsartan group	Difference with before treatment in control group	Z	P value
Creatinine(μmol/L)					
	6 months	0.40(0.21,0.67)	19.75(12.28,26.04)	−1.141	0.254
	12 months	1.50(0.98,2.07)	31.65(22.77,42.53)	−2.022	0.043
eGFR[ml/(min·1.73m^2)]					
	6 months	−2.19(1.07,3.51)	−14.71(9.86,21.55)	−1.873	0.061
	12 months	−2.21(1.33,3.49)	−22.11(12.32,29.67)	−2.280	0.023
BUN(mmol/L)					
	6 months	−2.62(1.83,3.90)	0.45(0.29,0.70)	−4.393	0.000
	12 months	−2.80(2.01,4.23)	0.80(0.58,1.14)	−4.640	0.000
Serum uric acid(μmol/L)					
	6 months	−137.00(−92.30,−201.13)	−9.65(49.00,−79.80)	−4.626	0.000
	12 months	−141.00(−96.40,−200.25)	−8.45(45.00,−77.70)	−4.628	0.000

eGFR: estimated glomerular filtration rate; BUN: blood urea nitrogen.

本研究中,2 组在治疗后 6 个月及 12 个月均出现不同程度的 WRF;对照组随访 0~6 个月和 6~12 个月分别有 7 例(19.44%)和 2 例(5.56%)的患者出现 WRF(0~12 个月共 25.00%),这与 COACH 研究[7]一致;但服药后 12 个月,沙库巴曲缬沙坦组 WRF 发生率显著低于对照组,考虑与沙库巴曲缬沙坦在 WRF 的发生机制上起到遏制作用有关[13]。首先通过血管紧张素Ⅱ受体拮抗剂选择性阻断 AT1 型受体、抑制 RAAS 系统激活,其次抑制脑啡肽酶导致利钠钛、缓激肽和肾上腺髓质激素水平持续升高。利钠钛具有扩张入球小动脉和出球小动脉作用,使肾小球囊内压升高,进而使 eGFR 增加,此外利钠钛还可以松弛肾系膜细胞,增加滤过面积及 eGFR,参与了肾小球血流动力学机制的调节,同时利钠肽可抑制肾素和血管紧张素Ⅱ激发的醛固酮释放,上调缓激肽和肾上腺髓质激素水平,抑制肾脏炎症、凋亡、纤维化、肾小球硬化和肾动脉硬化,保护肾功能[14]。研究表明与单独使用 RAAS 抑制剂相比,沙库巴曲缬沙坦延缓了 WRF,其对肾功能的保护作用随着用药时间的延长,优势越明显。

本研究还发现,沙库巴曲缬沙坦组心功能改善先于肾脏保护出现,血压降低和肾脏保护同步。心脏疾病的患者大多存在心肾共病现象,心肾综合征的概念越发受到重视,其机制包括了血流动力学机制及非血流动力学机制。慢性心肾综合征是由各种病因所致慢性心力衰竭引起心排血量下降,导致肾脏慢性低灌注,加之常伴有亚临床炎症及内皮细胞功能障碍,继发不同程度的肾功能损害[15],可见改善肾功能的首要任务为改善心功能。本研究结果证实了心功能的改善先于肾脏保护出现,符合Ⅱ型心肾综合征的发病机制及临床特征。沙库巴曲缬沙坦的降压机制包括增加 eGFR 及肾脏排钠排尿的肾性机制,促进血管舒张、抵抗血管收缩的血管机制以及抑制肾素、醛固酮释放及交感神经系统活性的神经内分泌机制,可见在降压的同时沙库巴曲缬沙坦就发挥了肾脏保护作用,与本研究结果一致。

综上,与单一缬沙坦相比,沙库巴曲缬沙坦减慢了合并肾功能不全的 HFrEF 患者肾功能不全的进展速度,推迟了 WRF 的时间,尿素氮及尿酸在随访初期即出现较大幅度的下降,后期下降幅度逐渐减少,但均优于单一缬沙坦。沙库巴曲缬沙坦可以延缓、控制肾功能的进行性恶化,为心肾共病的治疗提供新思路、新手段。

本研究存在一定的局限性,本研究仅评价了合并肾功能不全的 HFrEF 患者服药后 6 个月和 12 个月的肾功能变化情况,而其长期的影响尚不清楚。另外,本研究除外了 eGFR<15 ml/(min · 1.73m^2)及接受肾脏透析的患者,对于这部分患者是否可以接受沙库巴曲缬沙坦治疗及其对肾功能的影响尚待进一步探讨。

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