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INVESTIGATING THE IMPACT OF ROSUVASTATIN ON LIVER FUNCTION BY ASSESSING BIOMARKERS RELATED TO LIVER SYNTHESIS AND EXCRETION IN PATIENTS WITH CARDIOVASCULAR ATHEROSCLEROSIS

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ABSTRACT

Background: Rosuvastatin serve as a fundamental treatment for lowering the level of LPL-cholesterol, helping to prevent the risk of atherosclerosis cardiovascular disease that leads to death. This makes Rosuvastatin among the most widely prescribed medication classes globally. The liver-related side effects of Rosuvastatin are commonly characterized as an elevated risk of declining liver function that correlates with higher medication doses. Research indicates that Rosuvastatin -induced liver toxicity usually develops during the initial year of therapy.

Objective: To assessment the connection of Rosuvastatin treatment period on liver function activity in people diagnosed with atherosclerotic cardiovascular disease.

Method: The research spanned 24 weeks, with monitoring visits scheduled at weeks 1, 8, 16, and 24 to track changes in liver function parameters. The evaluation process incorporated clinical assessments and laboratory testing. To ensure reliable and consistent results, the study maintained rigorous protocols and assigned a dedicated technician to perform all evaluations.

Results: Six months following the start therapy with rosuvastatin in atherosclerotic patients result showed: significantly increase ($p<0.001$) with (ALT, AST, GGT), as a liver injury signs, and result showed as synthetic liver efficacy a relatively significant decrease ($p<0.001$) in: (Total protein (6.3, 6.2, 5.5, 4.6gm/dL), Albumin (4.2, 3.2, 3.0, 2.8gm/dL), Cholinesterase (10.6, 6.9, 6.5, 4.2 U/L), Prothrombin time showed a significant increase (9.6, 12, 12.8, 13.2) at the period (1,8, 16, and 24 weeks) respectively. Result also showed a significant increase in: Total Bilirubin (0.7, 1.9, 2.5, 3.2 mg/dL), Direct Bilirubin (0.2, 1.2, 1.8, 2.3 mg/dL), ALP (70, 86, 139, 142 U/L), as liver excretion efficacy. Rosuvastatin can cause a variety of changes in the mechanisms of liver function, but not real damage to liver cells and tissues. Although the exact mechanism is still unclear, it is likely related to an idiosyncratic drug-induced liver injury.

KEYWORDS: Rosuvastatin, atherosclerotic, liver toxicity, medication dose.

INTRODUCTION

Statins work by blocking 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which helps lower both total cholesterol and low-density lipoprotein (LDL) cholesterol levels[1]. Numerous controlled studies have proven that reducing LDL cholesterol, especially with statin treatment, substantially decreases cardiovascular death rates and related events[2]. Research has also confirmed that HMG CoA inhibitors can prevent atherosclerotic problems and subsequent heart complications in people with ischemic heart disease[3]. Rosuvastatin belongs to a group of hydrophilic[4] statins that show a stronger preference for liver tissue[5]. This medication uses active transport to enter cells and generally stays out of tissues outside the liver[6], making it particularly effective in elderly patients over 75 years old[7]. Research by Mostaza et al. showed that 10 mg/kg/day of rosuvastatin led to a 16% reduction in harmful atherosclerosis events[1]. While rosuvastatin successfully lowered cholesterol levels, studies found it also caused liver enzyme elevations[8][9]. We need to use careful judgment when prescribing rosuvastatin because its serious side effects might sometimes outweigh the benefits[10]. A separate study documented a 22% drop in major adverse atherosclerotic events. Both investigations observed mild liver enzyme increases with high-dose rosuvastatin, which raised questions about potential liver damage from statins[11]. Although statin-related liver toxicity occurs infrequently[12], using high-dose statins in heart patients continues to spark debate[13]. Numerous studies have examined how well statins work and their safety profile in people with atherosclerosis[14][15]. However, these research findings have limited broader application because they typically focus only on patients without considering their existing liver function[16]. To fill this research gap, we performed this study and collected data to explore the

relationship between Rosuvastatin treatment period and defective liver function. Chronic liver disease often shows no symptoms, and elevated liver enzymes may be the first sign of liver damage[17]. These concerns highlight the urgent need for an unbiased assessment of side effects linked to rosuvastatin use. Such evaluation is crucial for separating assumptions from real risks of statin therapy, especially regarding liver function. Our research specifically examines how effective and safe rosuvastatin (a water-soluble statin) is in elderly patients experiencing atherosclerosis.

MATERIAL AND METHODS

This clinical study enrolled Atherosclerotic Cardiovascular patients from the Baquba Laboratories accredited by the Iraqi Ministry of Health, throughout the period from March 2025 to September 2025. The principal standard for overall patients is as follows: age for patients (55 to 65 years), diagnosed with atherosclerotic cardiovascular disease. Exclusions: the patient had any symptom of chronic hepatic diseases, kidney disease, thyroid defect, viral hepatitis, or diabetes. Also, the clinical trial was approved for ethical approval, and all patients in the study provided their consent. All patients treated with a rosuvastatin dosage of 10 mg/kg /day for 24 weeks were evaluated and divided into four time periods (1, 8, 16, and 24). The assessment methodology followed four stages, during which therapeutic progress was monitored by tracking lipid profile levels for all patients. Venous blood from all patients was withdrawn at baseline and after the 1st, 8th, 16th, and 24th week. Serum was separated and aliquoted after centrifugation of the blood samples for 20 min and frozen at−20 °C to be stored until the assay time. Also, assessments for clinical and laboratory tests were included as a methodology recommended to be explained in table1.

Table 1.All methodology recommended for clinical parameter tests in the study.[18]

parameter	methodology
Alanine Aminotransferase (ALT)	Bergmeyer et al,1986
Aspartate Aminotransferase (AST)	Bergmeyer et al,1986
Gamma-Glutamyl Transferase (GGT)	Szasz et al,1976
Alkaline phosphatase (ALP)	colorimetric assay Method
Cholinesterase	Harper and Row, 1974
Albumin	DOUMAS B.T.1972
total protein	Biuret Method
bilirubin	Müller Method

Statistical Analysis

All indicators are reported as Mean ± SD. Statistical analysis of the results was performed using Statistical Package for the Social Sciences (SPSS) software version 26.0, along with Microsoft Excel 2016. The analysis utilized Analysis of Variance (ANOVA), and significant differences were assessed using Duncan's multiple range tests, with a significance level set at $P \leq 0.05$.

RESULT

The current study continued six months after the treatment with rosuvastatin (10 mg/kg/day). All abnormalities in the liver function tests at the 8th, 16th, and 24th week (endpoint) were statistically significant ($P \leq 0.05$).

1-Hepatocellular Injury Parameters

The values of biochemical measurements for the liver enzymes are shown in Table 2. [Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), and Gamma-Glutamyl Transferases (GGT) are considered to be markers of hepatocyte injury. The results showed increase levels enzymes in patients were given a drug compared with the initial test (before treatment). The results showed increase significant ($P \leq 0.05$) in ALT, AST, and GGT serum levels at the period (8, 16, and 24) weeks after treatment with rosuvastatin (10 mg/kg/day) compared to the initial test, which showed a normal level of ALT, AST, and GGT in serum($P \leq 0.05$).

Table (2): The level of hepatocellular injury parameters at the initial stage of the study, 8 weeks, 16 weeks, and 24 weeks after treatment with rosuvastatin (10 mg) daily.

Parameters*	Initial test Mean ± SD*	8 week Mean ± SD*	16thweek Mean ± SD*	24thweek Mean ± SD*	*P*-value
ALT (IU/L)	35 ± 0.66	66 ±0.65	110 ±0.80	224 ±0.72	p<0.001
AST (IU/L)	40 ± 0.48	78 ±0.40	96 ±0.23	140 ±0.30	p<0.001

GGT (IU/L)	**30 ± 0.09**	**60 ±0.12**	**63 ±0.08**	**77 ±0.15**	**p<0.001**

***Normal range: (ALT) = (5-40 IU/L), (AST) = (10-40 IU/L), and (GGT) = (8-60 IU/L) *Expresses data in the mean ±SD.P<0.05.**

Rosuvastatin-induced liver injury has been associated with both hepatocellular and cholesteric patterns of injury[19]. A hepatocellular pattern of liver injury is defined by a predominant rise in aminotransferases, more specifically, alanine aminotransferase (ALT)[20][5]. And this result agreed with Hayashi and Bjornson study.[21] Long-term treatment with Rosuvastatin elevated the risk of liver function decay, and this is called Rosuvastatin –induced liver toxicity, which develops over a long period of beginning treatment[22]. Our result in figre1, indicated the change in enzymes concentration during the time of treatment, this drug causes elevation of liver function test over time, and this similarity with by Glueck et al., who found these abnormalities are dose-dependent, a little derangement or no change in liver function with Rosuvastatin 5mg rather than 10mg which showed higher elevated when used for a long time [8]. While Kasliwal found a higher level of liver function tests when using 40mg of rosuvastatin daily [23]. Hepatocyte dysfunction or biliary duct diseases can cause an increase in GGT enzyme levels; therefore, the increase in GGT levels has been considered a premature and reactive marker of hepatocyte injury[24]. Previous studies have shown that a two-fold increase in liver enzymes compared to the limit can be an indicator for Rosuvastatin-induced hepatocyte injury [17][25]; thus, it is consistent with the result of our study, which suggested the increased levels of [ALT, AST, and GGT] enzymes, related to liver dysfunctions during treatment with Rosuvastatin.

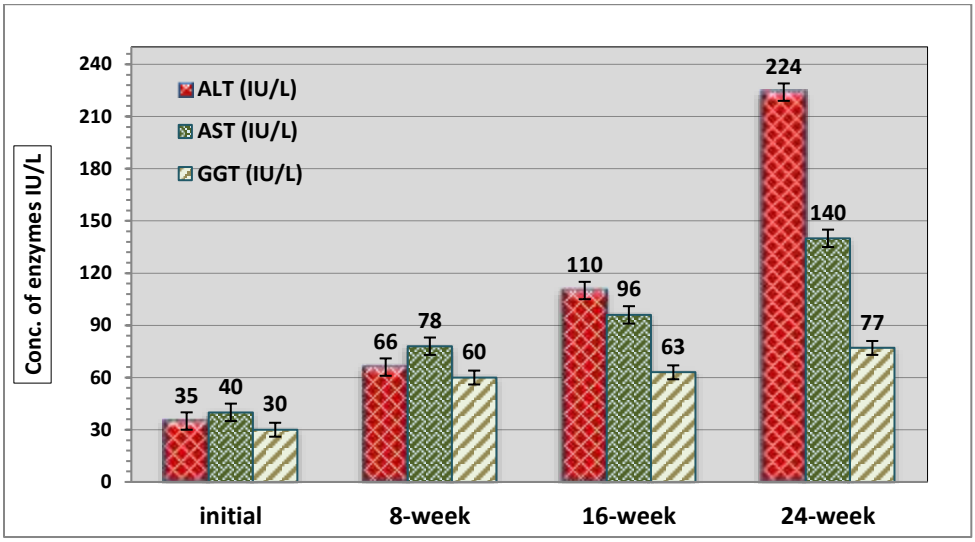

Figure-1- Rosuvastatin effect on: [(ALT), (AST), (GGT)] enzymes are considered to be markers of hepatocyte injury. At the initial stage of the study, 8 weeks, 16 weeks, and 24 weeks after treatment with rosuvastatin (10 mg/kg/day).

2- Liver Synthetic Capacity

The values of biochemical measurements for the serum and plasma of patients that are shown in Table(2) are considered to be markers of liver synthetic capacity. Results showed a low concentration of total protein and albumin in patients treated with rosuvastatin (10mg/kg/day) compared to the initial test (before treatment). Results showed a significant decrease (P≤0.05) in total protein and albumin serum levels at period (8, 16, and 24) weeks after treatment with Rosuvastatin compared with initial test, which showed a normal level of total protein and albumin in serum (P≤0.05). Also, statistical results showed increase significant (P≤0.05) in Prothrombin time serum levels at the period (8, 16, and 24 weeks) after being treated with Rosuvastatin compared with initial test, which showed a normal level of Prothrombin time in serum(P≤0.05). and this result is consistent with(Metwally et al.), who have found an association of Rosuvastatin with a decrease in the total proteins and albumin, which may be related to hepatic synthetic dysfunction[26].

Table (3). Levels of liver synthetic capacity parameters at the initial stage of the study, 8 weeks, 16 weeks, and 24 weeks after treatment with rosuvastatin (10 mg) daily.

Parameters*	**Initial test Mean ± SD***	**8 week Mean ± SD***	**16th week Mean ± SD***	**24th week Mean ± SD***	***P*-value**

Total protein (gm/dL)	**6.3±1.02**	**6.2±1.07**	**5.5±0.91**	**4.6±1.23**	**p<0.001**
Albumin (gm/dL)	**4.2±1.58**	**3.2±1.45**	**3.0±1.40**	**2.8±0.10**	**p<0.001**
Cholinesterase (U/L)	**10.6±2.07**	**6.9±1.82**	**6.5±1.03**	**4.2±0.96**	**p<0.001**
Prothrombin time(PT)	**8.6±0.16**	**10±1.05**	**11.8±1.36**	**13.2±1.11**	**p<0.001**

***Normal range: Total protein (6-8 gm/dL), Albumin (3.5-5.4gm/dL), Cholinesterase (8 -18 units/mL), Prothrombin time (9-12). *Expresses data in the mean ±SD.P<0.05.**

The results in Table 3 and Figure 2 showed a significant reduction (P≤0.05) in Cholinesterase serum levels at the period (8, 16, 24weeks) after treatment with Rosuvastatin (10mg/kg/day) compared to the initial test, which showed a normal level of Cholinesterase in serum(P≤0.05). The results were in similarity with the research by Pytel et al.) investigated the impact of lipid-lowering therapies (using rosuvastatin) on the activity of two enzymes, AChE and BChE, showing low affective in enzyme after treatment with rosuvastatin: 26% LDL level, 26% AChE and 18% BChE compared with control[3].

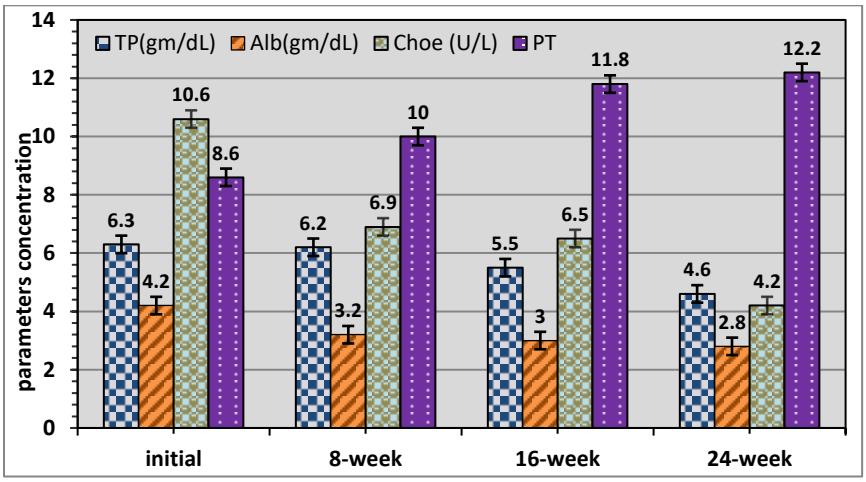

Figure-2- Rosuvastatin effect on liver synthetic capacity parameters: Total protein(TP), Albumin(Alb), Cholinesterase (ChE), Prothrombin time (PT) at the initial stage of the study, 8 weeks, 16 weeks, and 24 weeks after treatment with rosuvastatin(10 mg/kg/day).

The liver's biosynthetic capacity, reflected by serum albumin concentration, provides an indicator of hepatic function. Albumin measurement is often combined with prothrombin time to more comprehensively assess liver biosynthesis[27].Liver is the main manufactured of clotting factor ,therefore any dysfunction in liver synthetic ability can be led to prothrombin time prolongation [28]. In a previous study, rosuvastatin was associated with a reduction in platelet count, and it was the main cause of prothrombin time increase in patients with high LPL-cholesterol[29].

3- Liver Excretion Parameters

The values of biochemical measurements for the serum of patients are shown in Table 4 and Figure 3, which are considered to be markers of liver excretion capacity. Results showed a significant decrease (P≤0.05) in total, direct bilirubin serum levels at periods (8, 16, and 24) weeks after treatment with Rosuvastatin (10 mg/kg/day) compared to the initial test, which showed a normal level of total, direct bilirubin in serum (P≤0.05). Also, The statistical results showed a significant increase (P≤0.05) in alkaline phosphatase serum levels at the period (8, 16, and 24) weeks after treatment with Rosuvastatin (10 mg/kg/day) compared to the initial test, which showed a normal level of alkaline phosphatase in serum(P≤0.05), and results agreed with Shah,2019 showed rising in level of bilirubin and alkaline phosphates to17.2 mg/dL,277U/L respectively in patients with jaundice after six weeks for starting treatment with (5mg)of Rosuvastatin [30].

Table (4). Levels of liver excretion parameters at the initial stage of the study, 8 weeks, 16 weeks, and 24 weeks after treatment with rosuvastatin (10 mg/kg/ day).

Parameters*	**Initial test Mean ± SD***	**8 week Mean ± SD***	**16thweek Mean ± SD***	**24thweek Mean ± SD***	***P*-value**
Total Bilirubin(mg/dl)	**0.7± 0.05**	**1.9± 0.02**	**2.5± 0.04**	**3.2± 0.09**	**p<0.001**
Direct Bilirubin(mg/dl)	**0.2± 0.01**	**1.2± 0.06**	**1.8± 0.06**	**2.3± 0.17**	**p<0.001**

ALP (U/L)	**70 ± 0.22**	**86 ± 0.13**	**139 ± 0.41**	**142 ± 0.29**	**p<0.001**

***Normal range: Total Bilirubin (0.2-1.2 mg/dl), Direct Bilirubin (0.01-0.4mg/dL), ALP (40-130 U/L). *Expresses data in the mean ±SD.P<0.05.**

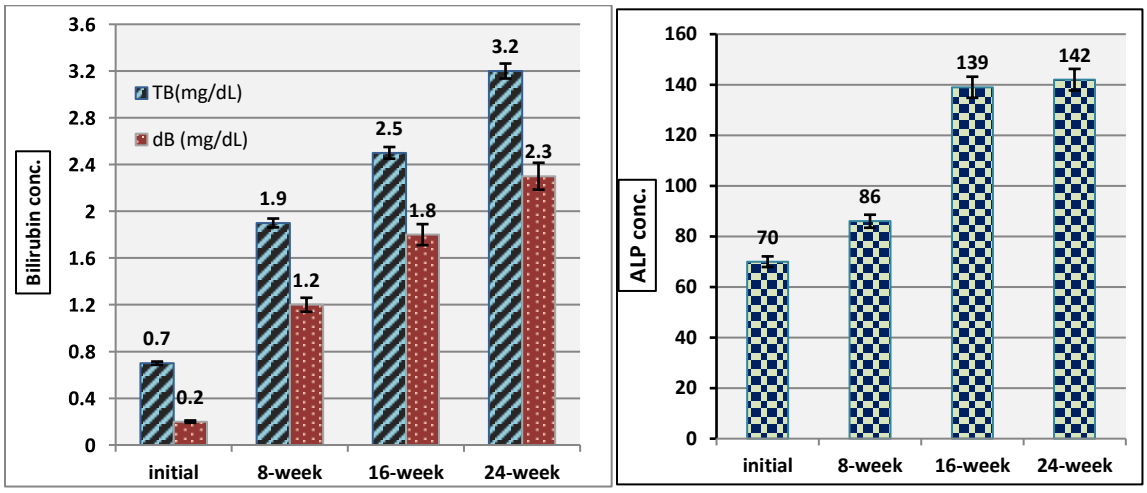

Figure-3- Rosuvastatin effect on liver excretion capacity parameters: Total Bilirubin, Direct Bilirubin at the (8 weeks, 16 weeks, and 24 weeks) after treatment with rosuvastatin (10 mg/kg/day).

Elevated levels of ALP and bilirubin usually signal liver damage. Alkaline phosphatase is issues in the bile ducts raise the enzyme level[31]. Previous studies showed developed jaundice after 15 weeks starting Rosuvastatin (10mg /kg/day)[32], and after 6weeks starting Rosuvastatin (5mg/kg/day) in a hypercholesterolemia patient[30]. It is important to check for medications and potential causes of liver toxicity. Previous studies recommended performing liver function tests before starting Rosuvastatin and again after 6 and 12 weeks of treatment [33]. However, the recently updated recommendations suggest that testing can happen between 4 and 12 weeks, and if patients show symptoms of liver damage, testing of total bilirubin and alkaline phosphatase is necessary for liver safety. [34]

DISCUSSION

Patients over 40 take rosuvastatin to lower the risk of complications from atherosclerotic disease. The main role of Rosuvastatin is to reduce LDL-cholesterol a proximally 55- 60%, making it the top choice for many patients. This research, mainly using data from controlled trials, offers insights into safety and tolerability[31]. The result of this study showed that treatment with Rosuvastatin affected liver functions compared to the initial tests before treatment. We found that administering rosuvastatin 10mg/kg/day for 24 weeks significantly influenced the levels of biomarkers related to liver function and detoxification in elderly cardiovascular atherosclerosis patients. Previous research indicated that rosuvastatin increases liver enzymes, and can led to physiological risk in liver tissues [35].

Alanine Aminotransferase and Aspartate Aminotransferase are mainly synthesized by hepatic cells. ALT, mainly found in the liver cells rather than AST, which is also found in limited amounts in the heart and muscle[36]. Our study supports that biomarkers, aminotransferases, which released from liver cells will be increased by any reason of liver cell injury. Thus, diagnosis of biomarkers can improve early treatment [37]. Many studies indicated that early diagnosis is even therapeutically beneficial[38]. GGT is an enzyme found in the liver and biliary tract, also in various organs (pancreas and kidney). It plays a role in glutathione metabolism in multiple tissues. An increase in GGT is usually significant for liver and biliary diseases, especially when it occurs alongside other elevated liver tests[39].

GGT levels can also rise due to medications. As a marker, it is highly sensitive to liver disease but lacks specificity[40]. Our study founded the treatment with rosuvastatin (10 mg/kg/day) increased serum levels of ALT, AST, and GGT after a long treatment period. In this study, the activities of serum total proteins and albumin levels decreased after Rosuvastatin treatment, suggesting potential hepatic injury[41]. Furthermore, the observed reduction in total proteins and albumin has been associated with liver damage[42]. Low serum albumin is an important indicator of chronic liver dysfunction[43]. Due to albumin's half-life of approximately 20 days, decreased serum levels reflect a prolonged failure in biosynthetic capacity rather than an acute injury[44]. In this study, treatment with rosuvastatin (10 mg/kg/day) increased serum levels of ALP, total bilirubin, and conjugated bilirubin after 24 weeks of treatment, That mean reduction in liver excretory function.[45].

Alkaline phosphatase is located in liver cells on the canalicular membrane, not in bile duct cells. Alkaline phosphatase typically rises due to increased synthesis of the enzyme in the canaliculus, which then moves to the sinusoid. Alkaline phosphatase is also a marker for liver disease[46]. When the bile ducts are obstructed, ALP level increases even though

it does not raise serum bilirubin levels in some obstructions[47]. The minor elevated the canalicular GGT enzyme can be an indicator of source alkaline phosphatase, which increases, comes from the liver[35].
Bilirubin is formed by the breakdown of old red blood cells. In the liver, conjugation by uridine 5'-diphospho (UDP)-glucuronosyltransferase makes conjugated bilirubin, allowing for its excretion in bile [48]. An elevated direct bilirubin level is significant. Fractionating total bilirubin is often helpful when ALT indicates liver cell dysfunction or cholestasis [49]. In a recent study, it was suggested if total bilirubin and ALP part levels rise, the drug must be stopped. Also should be re-measured this biomarkers after two to four weeks to determine whether to stop the rosuvastatin [50]. Cholinesterase's are important in the human body[51]. We also see a drop in BChE activity in conditions that show oxidative stress and those marked by lipid metabolism issues. It seems that decreased cholinesterase activity is more common[52].
Rosuvastatin is widely used as a suitable drug for the treatment of hyperlipidemia and improving cardiovascular atherosclerotic disease. Mainly, the side effects of Rosuvastin lead to hepatotoxicity. Our study is concerned by diagnosis and assessment of the increase in the incidence of liver injury after using rosuvastatin for a long-term for treatment, although Rosuvastatin has benefits that sufficiently outweigh the risk of side effects. Most ensure that Rosuvastatin will be used for the patients should be needed. The risk side effect can be prevented by suitable examination before treatment and during the period of drug treatment.

CONCLUSION

In elderly cardiovascular patients, Rosuvastatin is generally well-tolerated and can effectively improve lipid profiles and cardiac function without significant impairment of liver synthetic ability or detoxification processes. Monitoring typically focuses on liver enzymes as surrogate biomarkers for potential hepatotoxicity, though serious injury remains rare. Further study, including randomized clinical trials, is required to provide decisive evidence through validating these retrospective findings.

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