The Safety of The Directly Acting Antiviral Treatment For Hepatitis C Virus According To The Egyptian National Program Protocol In Patients With Midrange Ejection Fraction

Ahmed Farouk Alaarag1, Ahmed Mohamed Hamam2 and Osama Ahmed Amin3

1 Department of Cardiology Tanta University, EG
2 Department of Internal Medicine, Armed Forces College of Medicine, EG
3 Department of Cardiology, Beni Suef University, EG
Corresponding author: Ahmed Farouk Alaarag, MD (ahmed.elaarag@med.tanta.edu.eg)

Background: The Egyptian National Committee of Viral Hepatitis program is the leading national hepatitis C virus (HCV) management program globally. However, limited data is available about the effect of the new directly acting antiviral agents on the cardiovascular system.

Objectives: Our study aimed to assess the safety of the relatively new directly acting antiviral agents approved by the National Health Committee in Egypt to treat patients infected with hepatitis C virus who have midrange left ventricular ejection fraction.

Methods: This multicenter study included 400 successive patients with an ejection fraction (40–49%) from May 2017 to December 2019. We classified them into two groups: Group I (Child A), who received Sofosbuvir and Daclatasvir for twelve weeks, and Group II (Child B), who received Sofosbuvir, Daclatasvir, and Ribavirin for twelve weeks. Patients were evaluated for their symptoms, ejection fraction, brain natriuretic peptide, lipid profile, fasting blood glucose, fasting insulin, Homeostatic Model Assessment of Insulin Resistance levels, and Holter monitoring (just before the start of treatment and within three days after completing therapy).

Results: We found New York Heart Association Class, ejection fraction, brain natriuretic peptide, premature ventricular contractions burden, as well as highest and lowest heart rate did not show a statistically significant difference in both groups after treatment. The treatment did not cause bradycardia or non-sustained ventricular tachycardia. Fasting blood glucose and fasting insulin levels declined, with improved insulin resistance after treatment in both groups. Both low and high-density lipoprotein cholesterol increased after treatment in Group II.

Conclusions: Both regimens of directly acting antiviral agents used in Egypt to treat chronic hepatitis C virus infection are safe in patients with New York Heart Association Class I and II with midrange left ventricular ejection fraction (40–49%). There are beneficial metabolic changes following HCV clearance as an improvement of insulin resistance.

Keywords: Hepatitis C Virus; Directly Acting Antiviral Agents; Midrange Left Ventricular Ejection Fraction

Introduction
Hepatitis C virus (HCV) is a single-stranded ribonucleic acid (RNA) virus. HCV has a worldwide prevalence of 2.5% and infects 180 million people worldwide [1]. HCV infection in Egyptian people has high health, economic, and social burden. Egypt had the highest HCV prevalence globally. According to the Egyptian Demographic Health Survey (EDHS) in 2008, the prevalence rate of HCV infection in Egypt was 14.7% in the 15–59 year age group [2].
The Egyptian National Committee for Control of Viral Hepatitis (NCCVH) program is the world’s leading national HCV program. This screening and mass treatment program put Egypt on a fast track to HCV elimination, making it potentially the first country to achieve the WHO disease elimination targets [3].

Chronic HCV infection has been linked to subclinical and clinical cardiovascular diseases (CVD). The proposed mechanisms include chronic inflammation and immune activation driven by HCV infection as well as direct endothelial invasion and dysfunction, but no mechanism could be confirmed till now [1, 4].

Chronic HCV infection interferes with glucose and lipid metabolism, resulting in insulin resistance and diabetes mellitus (DM). The potential mechanism is to interfere with insulin signaling pathways related to increased tumor necrosis factor (TNF-α) and higher HCV viral load [1]. Also, HCV replication within liver cells may impact insulin and lipid metabolism. The changes in both can affect cardiac function by their effect on atherosclerosis [5, 6]. Furthermore, interferon (IFN) and the directly acting antiviral agents (DAAs) therapies significantly improved cardiovascular outcomes. However, limited data is available about the effect of the new DAAs on the cardiovascular system after virus eradication [7].

The patients with myocardial dysfunction were unable to tolerate IFN. The novel DAAs do not have the harmful effects of IFN on heart performance. Therefore, the relatively new drugs may offer a better chance for such patients to receive antiviral therapy [8].

There is no robust data for the safety of the novel DAAs used to treat chronic HCV with other comorbidities [8]. The lack of published evidence-based data on these agents’ safety in patients with cardiac dysfunction compelled the need for this study. Patients with heart failure and midrange ejection were selected to provide evidence on the safety of novel DAAs in this group of patients. The treating physicians excluded most patients with advanced heart failure due to shorter life expectancy and lack of safety evidence.

**Methods**

In this prospective multicenter study, we enrolled 400 chronic HCV patients with midrange LVEF (40% to 49%) [9] from May 2017 to December 2019. We selected them during the routine workup for HCV treatment according to the NCCVH protocol. All study patients signed written informed consent. The local research committees approved the study following the Declaration of Helsinki. The Committees of Research and Medical Ethics at Tanta University, Beni Suef University, and Kobry El Kobba Hospital approved the protocol with approval reference numbers 08/17, C52017, and 7-04/2017, respectively.

We included chronic HCV patients in our cohort cross-sectional study. All included patients were eligible for receiving treatment according to the NCCVH protocol for HCV with EF (40–49%) and NYHA functional Class I or II. All patients were taking standard evidence-based anti-heart failure treatment.

We categorized the patients into two groups based on the appropriate DAAs regimens for their Child-Pugh Class [10]. Group I (Child A) included 200 successive patients who were assigned to receive Sofosbuvir and Daclatasvir (SOF+ DCV) for twelve weeks. While, Group II (Child B) included 200 successive patients who were assigned to receive Sofosbuvir, Daclatasvir, and Ribavirin (SOF+DCV+ RBV) for twelve weeks. It is to be noted that five patients in Group I (2.5%) and three in Group II (1.5 %) were on statin therapy, which was stopped prior to initiation of antiviral therapy.

We excluded from our study any patients with advanced liver cirrhosis (bleeding esophageal varices, more than mild ascites on abdominal ultrasound or hepatic encephalopathy), autoimmune hepatitis, renal failure, diabetes mellitus, pregnancy, NYHA class III and IV or EF <40%, patients taking amiodarone, patients with bradycardia (heart rate below 60) and any patient who did not attend the follow-up visit.

The patients were assessed just before starting the treatment, at the follow-up visit within three days after the end of treatment, and at confirmation of virus clearance (after three months). We evaluated the patients’ heart failure state by NYHA Class [11] and BNP levels. We also assessed EF using the M mode by the Teicholz formula. 2D mode by the biplane Simpson method was utilized when there were regional wall motion abnormalities (RWMAs) [12]. To reduce the inter-observer variability, the average of two operators’ measures of the EF were used. Additionally, the cardiologists doing echocardiography during the follow-up did not know the previous EF before starting treatment. We performed resting ECG and Holter monitoring for 24 hours. The laboratory assessment included aspartate amino transferase (AST), alanine amino transferase (ALT), serum bilirubin, serum albumin, prothrombin time (PT), international normalized ratio (INR), and HCV RNA by polymerase chain reaction (PCR). Further, patients’ metabolic profile were assessed by serum creatinine, lipid profile, 8-hour fasting blood glucose (FBG) level, 8-hours fasting insulin level, and the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR). Insulin Resistance was diagnosed if the HOMA-IR was equal to or greater than 2.7 [13] using the formula: HOMA-IR = fasting insulin in mIU/L x fasting glucose in mg/dL/405.
Statistical analysis
The baseline demographic and cardiometabolic characteristics were defined according to the HCV treatment regimen. They were tested for normal distribution using the Kolmogorov-Smirnov test. The continuous variables were presented as mean ± standard deviation (SD) and categorical variables were presented as proportions. The associations between baseline characteristics at follow-up were assessed using the chi-squared test for categorical variables and student t-test for continuous variables.

One-way analysis of variance (ANOVA) and chi-square tests were used to assess the distributions of numeric and categorical variables, respectively, across groups (before and after 12 weeks). Those characteristics statistically associated with the outcome of interest in the two groups after treatment were compared using a post-hoc test (LSD) for numeric variables and the chi-squared test for categorical variables to identify potential cardiometabolic risk factors associated with HCV treatment.

Wilks’ lambda multivariate test was used to evaluate the significance of the changes in studied parameters after HCV eradication and Levene’s test was used to assess data homogeneity. When changes were significant, and data were homogenous, general linear model (GLM) repeated measures tests and profile plots were conducted to compare these changes between the studied groups.

The power of sample size was estimated using g*power software 3.1.9.4, adjusted to a power of 80%, medium effect size, α error probability 0.05 for different variables. All analyses were done with 95% confidence intervals (95% CI) and considered a 2-tailed P value < 0.05 to be statistically significant. IBM SPSS software package version 21.0.0 was used for data analysis.

Results
Four hundred patients with chronic HCV infection and midrange EF (40% to 49%) were included in this cross-sectional cohort study. The patients were divided into two groups according to their DAA regimens and Child-Pugh classification. Group I (Child A) includes 200 patients who received (SOF+DCV) for twelve weeks. Group II (Child B) includes 200 patients who received (SOF+DCV+ RBV) for twelve weeks.

In our study 234 patients (58.5%) were men and 166 patients (41.5%) were women. Their mean age was 47.40 (±10.20) years. There was no significant difference between the patients in the two groups regarding age, gender incidence of hypertension, smoking, and NYHA Class: t = 1.227, P = 0.221 and X² = 0.515, P = 0.473; X² = 0.113, P = 0.203; X² = 0.358, P = 0.550 and X² = 2.918, P = 0.088 respectively. Also, there was no significant difference in either group regarding cardiac drug history, as shown in Table 1.

The DAAs did not affect patients’ clinical, echocardiographic, or laboratory parameters of heart failure in either group, as measured by NYHH class, EF, and BNP, respectively, as shown in Table 2. Also, DAAs in both groups did not produce any significant increase in the incidence of arrhythmias, with no significant difference in PVCs burden, highest and lowest heart, bradycardia, and non-sustained ventricular tachycardia (VT), as shown in Table 3.

Table 1: Comparing basal demographic data and cardiac drug history of Group I and Group II.

|                      | Group I       | Group II      | t/X²   | P    |
|----------------------|---------------|---------------|--------|------|
| Age (Years)          | 48.28 ± 11.89 | 46.51 ± 8.463 | 1.227* | 0.221|
| Males (%)            | 112 (56%)     | 122 (61%)     | 0.515* | 0.473|
| Hypertension (%)     | 163 (81.5%)   | 165 (82.5%)   | 0.113* | 0.203|
| Smoking (%)          | 66 (33.0%)    | 60 (30.0%)    | 0.358* | 0.550|
| NYHA I (%)*          | 166 (83%)     | 146 (73%)     | 2.918* | 0.088|
| Beta Blockers (%)    | 174 (87%)     | 168 (84%)     | 1.337* | 0.247|
| ACEI/ARBs (%)        | 184 (92%)     | 188 (94%)     | 0.915* | 0.261|
| Diuretics (%)        | 96 (48%)      | 100 (50%)     | 0.824* | 0.367|
| Mineralocorticoids inhibitors (%) | 14 (7%) | 16 (8%) | 0.016* | 0.942|
| Digoxin (%)          | 8 (4%)        | 10 (5%)       | 0.116* | 0.733|

* NYHA I and NYHA II only included.
# Heart Rate (HR) < 60 b/min on resting ECG.
t Independent-Samples T-test.
X Chi-Square test.
HTN Hypertension.
There was a statistically significant decline in the FBG and improvement in insulin resistance after treatment in both groups, as shown in Table 4, Figures 1 and 2.

The general linear model (GLM) repeated measures tests were used to compare these changes in both groups. The FBG, FI and IR significantly declined after HCV eradication in both groups, Wilks' lambda = 0.971, 0.899 and 0.902 respectively, F = 4.799, 22.184 and 21.503 respectively and P = 0.048, <0.001 and <0.001 respectively. However, when comparing these changes between both groups, there were no significant differences, as shown in Table 5 and Figure 4.

In Group I, the total cholesterol, LDL-C, HDL-C, and triglycerides increased after treatment with no statistically significant difference, P = 0.068, 0.109, 0.619, and 0.140, respectively, as shown in Table 4 and Figure 3. In Group II, the LDL-C and HDL-C increased significantly after treatment, P = 0.028 and 0.019, respectively, as shown in Table 4 and Figure 3.
Table 4: Comparing fasting blood glucose, fasting insulin level, HOMA-IR and lipid profile in Groups I and II at Day 0 (baseline) and after three months (end of treatment).

|                      | Group I – 0  | Group I – 3  | Group II – 0 | Group II – 3 | F         | P          |
|----------------------|--------------|--------------|--------------|--------------|-----------|------------|
| FBG (mg/dl)          | 92.30 ± 12.14| 88.36 ± 10.27| 93.38 ± 12.50| 87.81 ± 10.47| 5.998     | 0.001\(^1\) 0.015\(^1\) 0.001\(^2\) |
| FI (uIU/ml)          | 11.18 ± 4.50 | 9.82 ± 3.61  | 12.65 ± 5.31 | 11.01 ± 3.98 | 6.960     | <0.001\(^1\) 0.030\(^1\) 0.008\(^2\) |
| HOMA-IR              | 2.56 ± 1.10  | 2.15 ± 0.85  | 2.90 ± 1.26  | 2.37 ± 0.86  | 9.414     | <0.001\(^1\) 0.005\(^1\) 0.001\(^2\) |
| Chol (mg/dl)         | 200.75 ± 45.16| 213.19 ± 49.51| 231.77 ± 41.59| 239.34 ± 54.69| 13.361    | <0.001\(^1\) 0.068\(^1\) 0.265\(^2\) |
| LDL-C (mg/dl)        | 127.14 ± 36.91| 134.95 ± 43.59| 129.16 ± 25.41| 140.21 ± 29.63| 2.867     | 0.036\(^1\) 0.109\(^1\) 0.028\(^2\) |
| HDL-C (mg/dl)        | 44.69 ± 8.59 | 45.22 ± 7.65 | 37.06 ± 6.20 | 39.57 ± 7.51 | 27.794    | <0.001\(^1\) 0.619\(^1\) 0.019\(^2\) |
| TGs (mg/dl)          | 141.98 ± 45.72| 151.98 ± 37.31| 159.58 ± 58.03| 166.39 ± 48.08| 4.792     | 0.003\(^1\) 0.140\(^1\) 0.315\(^2\) |

\(^1\) Post hoc test – least significant difference (LSD) between Group 1 – 0 and Group 1 – 3.
\(^2\) Post hoc test – least significant difference (LSD) between Group 2 – 0 and Group 2 – 3.

FBG: Fasting Blood Glucose; FI: Fasting Insulin; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; Chol: Total Cholesterol; TGs: Triglycerides.

Figure 1: Fasting blood glucose and fasting insulin levels at baseline and after three months in Groups I and II. FBG: Fasting blood glucose; FI: Fasting insulin.
Discussion

Cardiovascular disorders and HCV infection have a high prevalence in the general population. Both have a high incidence in middle and old age populations. HCV infection was claimed to be a non-traditional risk factor for many cardiac conditions such as coronary artery disease, cardiomyopathies, and cardiac arrhythmias. Also, the heart could be affected by antiviral therapy [14].

The natural history of chronic HCV infection is characterized by developing several extra-hepatic manifestations that cause increased morbidity and mortality [15]. The wide variety of such manifestations has been defined as ‘HCV syndrome’ [16]. HCV syndrome denotes the clinical expression of the organic effects of HCV [17].

D’Agostino et al. [18] found that HCV infection surges cardiovascular hazards, including heart failure. Reda et al. [19] found that DAAs did not cause EF changes or new RWMAs in patients with normal baseline EF [14]. Our study found that DAAs in patients with midrange LVEF did not worsen their NYHA functional Class or EF by the end of treatment after three months. Also, there was a mild nonsignificant decrease in BNP. These results occurred in patients who received dual and triple DAAs. In our study, the DAAs did not produce any significant increase in the incidence of bradycardia, non-sustained VT, PVCs burden, or in highest and lowest heart rate.

We excluded the patients treated with amiodarone because DAAs may increase its concentration by inhibiting intestinal cytochrome P450 3A4 [20]. Similarly, a randomized study of 50 patients with structurally
Figure 3: LDL-C and HDL-C levels at baseline and after three months in Groups I and II. LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol.

Figure 4: Changes in FBG, FI, and HOMA-IR levels at baseline and after three months in Groups I and II. FBG: Fasting Blood Glucose, FI: Fasting Insulin, HOMA-IR: Homeostatic Model Assessment of Insulin Resistance index, P1: Changes within groups, P2: Changes between groups.
normal hearts treated with (SOF+ DCV) showed no significant effect on rhythm, heart rate, heart rate variability, or conductivity [21]. A meta-analysis including nearly 2300 HCV patients treated with SOF found that SOF was not associated with arrhythmias or significant bradycardias [22].

Some studies found a reduction of total cholesterol, decreased LDL levels, and a worsening of glucose metabolism in HCV infection [23, 24]. Other studies described the impact of DAAs on glucose and lipid metabolism, and available data are incomplete and conflicting [25, 26]. Hashimoto et al. [27] suggested that DAAs lead to a significant increase in LDL. This negative impact is absent in IFN-based therapy cases, probably due to the frequent presence of anorexia [28].

Badawi et al. [29] reported that serum levels of triglycerides, LDL-C total cholesterol, and ApoB were significantly lower in HCV patients. Also, Batsaikhan et al. [30] found that viral clearance was associated with a significantly increased triglycerides level at six months after treatment. However, this elevation was not detected in patients with non-sustained virological response (SVR). At the same time, Tran et al. [31] found improvement in serum triglycerides level, especially in patients with baseline elevation. They found a mean reduction of serum triglycerides by 28.6 mg/dl in all patients after eight weeks of treatment and reduction by 60.4 mg/dl in those who had baseline elevation. They also showed that 61% of patients with triglycerides elevation at baseline had levels below 175 mg/dl by the end of treatment.

In our data, the total cholesterol, HDL-C, LDL-C, and triglycerides increased after virus clearance. In this context, Khattab et al. [32] stated that the degree of changes in the lipid profile was affected by the degree of recovery of hepatic fibrosis. Its elevation after treatment is an indicator of the recovery of the liver cells and improved liver function. Moreover, the more advanced the hepatic affection before treatment, the more elevation occurs after viral clearance. The changes in the lipid profile are not a direct effect of the drug on lipid metabolism.

HCV utilizes the lipid metabolic pathways during replication leading to lipid profile changes [33]. It circulates in the blood within lipoproteins, known as lipoviroparticles. Lipoviroparticles, which utilize LDL-C, protect HCV from neutralization [34]. Also, Chronic hepatitis C is associated with metabolic complications like insulin resistance that may progress to type 2 diabetes, hepatic steatosis, and hypobetalipoproteinemia [35].

By the end of DAAs-based treatment, the HCV clearance leads to changes in peripheral and intrahepatic metabolic pathways [36]. The serum LDL-C surge levels likely reflect a shift in lipid metabolism due to inhibition of HCV replication [37].

In our study, the cure from HCV infection resulted in improved IR, which is consistent with the findings of Lim et al. and El Sagheer et al. [38, 39]. Additionally, these findings mention that HCV infection treatment improved overall, hepatic, and adipose tissue insulin sensitivity.

The impact of HCV infection on IR could be explained in different ways, most of which involving insulin signaling [40, 41, 42]. The potential mechanisms include the degradation of insulin receptor substrate-1 (IRS-1), insulin activity inhibition, increased glucose synthesis, and release from hepatocytes [43] as well as hepatic inflammation and the production of pro-inflammatory cytokines (interleukin 8 & 18, tumor necrosis factor-alfa) increase IR in muscles and visceral fat [44]. Hence, HCV patients have a greater possibility of IR and type 2 diabetes mellitus than their matched non-HCV counterparts [45, 46].

Finally, the metabolic changes in patients with HCV can affect their prognosis by modifying their cardiovascular risk factors independent of the direct virus effect on hepatic cells and the development of liver cirrhosis or hepatocellular carcinoma. However, the long-term effects of DAAs and virus clearance on metabolic profile and its clinical significance of these statistically significant changes, as shown in some studies, need to be followed over a more extended period.

Conclusion
Both regimens of DAAs used in Egypt to treat patients with chronic HCV infection are safe in patients with NYHA functional Class I and II with midrange LVEF (40–49%). There are beneficial metabolic changes that occur with HCV clearance as an improvement of IR. On the other hand, attention should be paid to lipid profile changes, which can aggravate atherosclerosis and affect cardiac function negatively. Further research on a larger scale of heart failure patients and a more extended follow-up period is recommended.

Study limitations
A relatively small number of patients were included in this cross-sectional study. Not included were diabetic patients, patients with severely reduced EF, nor patients with NYHA class III and IV. A more extended follow-up period may be addressed in further studies to assess the more prolonged effects of the DAAs. Finally, while this study looked at the systolic function, the effect of DAAs on other echocardiographic parameters may be tested in further studies.
Data Accessibility Statements
The datasets used and or analyzed during the current study are available from the corresponding author on reasonable request.

Abbreviations
- 2D: Two Dimensions
- ALT: Alanine-Amino-Transferase
- AST: Aspartate-Amino-Transferase
- BNP: B-natriuretic peptide
- CHF: Congestive Heart Failure
- DAAs: Directly Acting Antiviral Agents
- DCV: Daclatasvir
- EDHS: Egyptian Demographic Health Survey
- LVEF: Left Ventricular Ejection Fraction
- FBG: Fasting Blood Glucose
- HCV: Hepatitis C Virus
- HDL-C: High-Density Lipoprotein – Cholesterol
- HOMA-IR: Homeostatic Model Assessment of Insulin Resistance
- INF: Interferon
- INR: International Normalized Ratio
- IR: Insulin Resistance
- LDL-C: Low-Density Lipoprotein – Cholesterol
- LV: Left Ventricle
- NCCVH: National Committee for Control of Viral Hepatitis
- NYHA: New York Heart Association
- PCR: Polymerase Chain Reaction
- PT: Prothrombin Time
- RBV: Ribavirin
- RNA: Ribonucleic Acid
- RWMAs: Regional Wall Motion Abnormalities
- SOF: Sofosbuvir
- SVR: Sustained Virological Response
- VT: Ventricular Tachycardia

Ethics and Consent
The Committee of Research, And Medical Ethics Of The Cardiology Department, Beni Suef University approved the study protocol (reference C52017) in March 2017. The Committee of Research, Tanta University, approved the protocol in April 2017. The Committee of Medical Ethics, Kobry El Kobba Hospital approved the protocol in April 2017. We obtained informed written consent from all the patients.

Acknowledgement
We want to thank our colleagues in the cardiology department, Beni Suef, and Tanta University for performing Echocardiography as a second observer.

Competing Interests
The authors have no competing interests to declare.
Author Contributions
AA Followed the patients, performed echocardiography and Holter at Tanta University, and edited the manuscript. OA Followed the patients for their cardiac symptoms, performed echocardiography and Holter at Beni Suef University, and edited the manuscript. AH Followed the patients and revised their laboratory data, collected all data, and performed the statistical analysis for our study. All the authors read and approved the final manuscript.

References
1. Babiker A, Hassan M, Muhammed S, et al. Inflammatory and cardiovascular diseases biomarkers in chronic hepatitis C virus infection: A review. Clin Cardiol. 2020; 43(3): 222–234. DOI: https://doi.org/10.1002/clc.23299
2. Elgharably A, Gomaa AI, Crossey MM, Norsworthy PJ, Waked I, Taylor-Robinson SD. Hepatitis C in Egypt – past, present, and future. Int J Gen Med. 2016; 10: 1–6. Published 2016 Dec 20. DOI: https://doi.org/10.2147/IJGM.S119301
3. Abdel-Razek W, Hassany M, El-Sayed MH, et al. Hepatitis C Virus in Egypt: Interim report from the world’s largest national program. Clin Liver Dis (Hoboken). 2020; 14(6): 203–206. Published 2020 Jan 29. DOI: https://doi.org/10.1002/cld.868
4. Vassalle C, Petta S, Pepe A, Craxi A, Bondin M, Cacoub P. Expert opinion on managing chronic HCV in patients with cardiovascular disease. Antivir Ther. 2018; 23(Suppl 2): 35–46. DOI: https://doi.org/10.3851/IMP3248
5. Felmlee DJ, Hafirassou ML, Lefevre M, Baumert TF, Schuster C. Hepatitis C virus, cholesterol and lipoproteins – impact for the viral life cycle and pathogenesis of liver disease. Viruses. 2013; 5(5): 1292–1324. Published 2013 May 23. DOI: https://doi.org/10.3390/v5051292
6. Milner KL, van der Poorten D, Trenell M, et al. Chronic hepatitis C is associated with peripheral rather than hepatic insulin resistance. Gastroenterology. 2010; 138(3): 932–941.e3. DOI: https://doi.org/10.1053/j.gastro.2009.11.050
7. Dalbeni A, Romano S, Bevilacqua M, et al. Beneficial effects of DAAs on cardiac function and structure in hepatitis C patients with low-moderate liver fibrosis. J Viral Hepat. 2020; 27(11): 1214–1221. DOI: https://doi.org/10.1111/jvhe.13355
8. Poller W, Haghikia A, Kasner M, et al. Cardiovascular involvement in chronic hepatitis C virus infections – insight from novel antiviral therapies. J Clin Transl Hepatol. 2018; 6(2): 161–167. DOI: https://doi.org/10.14218/JCTH.2017.00057
9. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC [published correction appears in Eur Heart J. 2016 Dec 30]. Eur Heart J. 2016; 37(27): 2129–2200. DOI: https://doi.org/10.1093/eurheartj/ehw128
10. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973; 60(8): 646–649. DOI: https://doi.org/10.1002/bjs.1800600817
11. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013; 62(16): e147–e239. DOI: https://doi.org/10.1016/j.jacc.2013.05.019
12. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging [published correction appears in Eur Heart J Cardiovasc Imaging. 2016Apr;17(4):412] [published correction appears in Eur Heart J Cardiovasc Imaging. 2016Sep;17(9):969]. Eur Heart J Cardiovasc Imaging. 2015; 16(3): 233–270. DOI: https://doi.org/10.1093/ehjci/jev014
13. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: Insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985; 28(7): 412–419. DOI: https://doi.org/10.1007/BF00280883
14. Domont F, Cacoub P. Chronic hepatitis C virus infection, a new cardiovascular risk factor? Liver Int. 2016; 36(5): 621–627. DOI: https://doi.org/10.1111/liv.13064
15. Schiavinato A, Zanetto A, Pantano G, et al. Polyclonal and monoclonal B lymphocytes response in HCV-infected patients treated with direct-acting antiviral agents. J Viral Hepat. 2017; 24(12): 1168–1176. DOI: https://doi.org/10.1111/jvh.12746

16. Ferri C, Antonelli A, Mascia MT, et al. HCV-related autoimmune and neoplastic disorders: The HCV syndrome. Dig Liver Dis. 2007; 39(Suppl 1): S13–S21. DOI: https://doi.org/10.1016/S1590-8658(07)80005-3

17. Spinelli JJ, Lai AS, Krajen M, et al. Hepatitis C virus and risk of non-Hodgkin lymphoma in British Columbia, Canada. Int J Cancer. 2008; 122(3): 630–633. DOI: https://doi.org/10.1002/ijc.23105

18. D’Agostino RB Sr, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008; 117(6): 743–753. DOI: https://doi.org/10.1161/CIRCULATIONAHA.107.699579

19. Biomy R, Abdelshafy M, Abdelmonem A, Abu-Elenin H, Ghaly G. Effect of chronic hepatitis C virus treatment by combination therapy on cardiovascular system. Clin Med Insights Cardiol. 2017; 11: 1179546817713204. Published 2017 Jun 22. DOI: https://doi.org/10.1177/1179546817713204

20. Zahno A, Brecht K, Morand R, et al. The role of CYP3A4 in amiodarone-associated toxicity on HepG2 cells. Biochem Pharmacol. 2011; 81(3): 432–441. DOI: https://doi.org/10.1016/j.bcp.2010.11.002

21. El Missiri AM, Rayan MM, Awad MM, El Desoky AI. Assessing the impact of a combination of sofosbuvir and daclatasvir treatment for hepatitis C virus infection on heart rate, rhythm and heart rate variability using 24-hour ECG monitoring. Egypt Heart J. 2020; 72(1): 37. Published 2020 Jul 1. DOI: https://doi.org/10.11014/s40344-020-00070-4

22. Caldeira D, Rodrigues FB, Duarte MM, et al. Cardiac harms of sofosbuvir: Systematic review and meta-analysis. Drug Saf. 2018; 41(1): 77–86. DOI: https://doi.org/10.1007/s40264-017-0586-2

23. Bugianesi E, Salamone F, Negro F. The interaction of metabolic factors with HCV infection: does it matter? J Hepatol. 2012; 56(Suppl 1): S56–S65. DOI: https://doi.org/10.1016/S0148-8871(12)60007-5

24. Gitto S, Cicero AFG, Loggi E, et al. Worsening of serum lipid profile after direct acting antiviral treatment. Ann Hepatol. 2018; 17(1): 64–75. DOI: https://doi.org/10.5604/01300010.0100.7536

25. Mauss S, Berger F, Wehmeyer MH, et al. Effect of antiviral therapy for HCV on lipid levels. Antivir Ther. 2017; 21(1): 81–88. DOI: https://doi.org/10.3851/IMP3094

26. Meissner EG, Lee YJ, Osnusi A, et al. Effect of sofosbuvir and ribavirin treatment on peripheral and hepatic lipid metabolism in chronic hepatitis C virus, genotype 1-infected patients. Hepatology. 2015; 61(3): 790–801. DOI: https://doi.org/10.1002/hep.27424

27. Hashimoto S, Yatsuhashi H, Abiru S, et al. Rapid increase in serum low-density lipoprotein cholesterol concentration during hepatitis C interferon-free treatment. PLoS One. 2016; 11(9): e0163644. Published 2016 Sep 28. DOI: https://doi.org/10.1371/journal.pone.0163644

28. Vezali E, Aghemo A, Colomb M. A review of the treatment of chronic hepatitis C virus infection in cirrhosis. Clin Ther. 2010; 32(13): 2117–2138. DOI: https://doi.org/10.1016/j.clinthera.2010.07.007

29. Badawi A, Di Giuseppe G, Arora P. Cardiovascular disease risk in patients with hepatitis C infection: Results from two general population health surveys in Canada and the United States (2007–2017). PLoS One. 2018; 13(12): e0208839. Published 2018 Dec 12. DOI: https://doi.org/10.1371/journal.pone.0208839

30. Batsaikhan B, Huang Cl, Yeh ML, et al. The effect of antiviral therapy on serum lipid profiles in chronic hepatitis C. Oncotarget. 2018; 9(30): 21313–21321. Published 2018 Apr 20. DOI: https://doi.org/10.18632/oncotarget.25092

31. Tran TT, Mehta D, Mensa F, Park C, Bao Y, Sanchez Gonzalez Y. Pan-genotypic hepatitis C treatment with glecaprevir and pibrentasvir for 8 weeks resulted in improved cardiovascular and metabolic outcomes and stable renal function: A post-hoc analysis of phase 3 clinical trials. Infect Dis Ther. 2018; 7(4): 473–484. DOI: https://doi.org/10.1007/s40121-018-0218-x

32. Khattab MA, Eslam M, Aly MM, et al. Serum lipids and chronic hepatitis C genotype 4: interaction and significance. Ann Hepatol. 2012; 11(1): 37–46. DOI: https://doi.org/10.1016/S1665-2681(19)31484-X

33. Cheng FK, Torres DM, Harrison SA. Hepatitis C and lipid metabolism, hepatic steatosis, and NAFLD: Still important in the era of direct acting antiviral therapy? J Viral Hepat. 2014; 21(1): 1–8. DOI: https://doi.org/10.1111/j.vhh.12172

34. Scheel TK, Rice CM. Understanding the hepatitis C virus life cycle paves the way for highly effective therapies. Nat Med. 2013; 19(7): 837–849. DOI: https://doi.org/10.1038/nm.3248
35. Felmlee DJ, Hafirassou ML, Lefevre M, Baumert TF, Schuster C. Hepatitis C virus, cholesterol and lipoproteins–impact for the viral life cycle and pathogenesis of liver disease. *Viruses*. 2013; 5(5): 1292–1324. Published 2013 May 23. DOI: https://doi.org/10.3390/v5051292

36. Kohli A, Shaffer A, Sherman A, Kottilil S. Treatment of hepatitis C: A systematic review. *JAMA*. 2014; 312(6): 631–640. DOI: https://doi.org/10.1001/jama.2014.7085

37. Meissner EG, Lee YJ, Osinusi A, et al. Effect of sofosbuvir and ribavirin treatment on peripheral and hepatic lipid metabolism in chronic hepatitis C virus, genotype 1-infected patients. *Hepatology*. 2015; 61(3): 790–801. DOI: https://doi.org/10.1002/hep.27424

38. Lim TR, Hazlehurst JM, Oprescu AI, et al. Hepatitis C virus infection is associated with hepatic and adipose tissue insulin resistance that improves after viral cure. *Clin Endocrinol (Oxf)*. 2019; 90(3): 440–448. DOI: https://doi.org/10.1111/cen.13924

39. El Sagheer G, Soliman E, Ahmad A, Hamdy L. Study of changes in lipid profile and insulin resistance in Egyptian patients with chronic hepatitis C genotype 4 in the era of DAAs. *Libyan J Med*. 2018; 13(1): 1435124. DOI: https://doi.org/10.1080/19932820.2018.1435124

40. Gualerzi A, Bellan M, Smirne C, et al. Improvement of insulin sensitivity in diabetic and non diabetic patients with chronic hepatitis C treated with direct antiviral agents. *PLoS One*. 2018; 13(12): e0209216. Published 2018 Dec 20. DOI: https://doi.org/10.1371/journal.pone.0209216

41. Negro F. HCV infection and metabolic syndrome: Which is the chicken and which is the egg? *Gastroenterology*. 2012; 142(6): 1288–1292. DOI: https://doi.org/10.1053/j.gastro.2011.12.063

42. Knobler H, Malnick S. Hepatitis C and insulin action: An intimate relationship. *World J Hepatol*. 2016; 8(2): 131–138. DOI: https://doi.org/10.4254/wjh.v8.i2.131

43. Kawaguchi T, Yoshida T, Harada M, et al. Hepatitis C virus down-regulates insulin receptor substrates 1 and 2 through up-regulation of suppressor of cytokine signaling 3. *Am J Pathol*. 2004; 165(5): 1499–1508. DOI: https://doi.org/10.1016/S0002-9440(10)63408-6

44. Knobler H, Zhornicky T, Sandler A, Haran N, Ashur Y, Schattner A. Tumor necrosis factor-alpha-induced insulin resistance may mediate the hepatitis C virus-diabetes association. *Am J Gastroenterol*. 2003; 98(12): 2751–2756. DOI: https://doi.org/10.1111/j.1572-0241.2003.08728.x

45. Calzadilla-Bertot L, Vilar-Gomez E, Torres-Gonzalez A, et al. Impaired glucose metabolism increases risk of hepatic decompensation and death in patients with compensated hepatitis C virus-related cirrhosis. *Dig Liver Dis*. 2016; 48(3): 283–290. DOI: https://doi.org/10.1016/j.dld.2015.12.002

46. White DL, Ratziu V, El-Serag HB. Hepatitis C infection and risk of diabetes: A systematic review and meta-analysis. *J Hepatol*. 2008; 49(5): 831–844. DOI: https://doi.org/10.1016/j.jhep.2008.08.006