Pharmacological interactions in novel oral anticoagulants, statins, and hypertension drugs in patients treated with direct-acting antivirals for hepatitis C: a Delphi Consensus project

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ABSTRACT

To date, no retrospective or real-world studies have comprehensively examined the interactions between direct-acting antivirals (DAAs) and widely used medications such as novel oral anticoagulant, statins, and antihypertensive agents. However, clinical experience from key opinion leaders may guide physicians in managing these interactions in patients undergoing DAA treatment. This study aims to elucidate the interactions between DAAs and commonly prescribed drugs in patients with prevalent comorbidities (*e.g.*, type II diabetes, hypertension, and dyslipidemia), with a particular focus on those receiving polytherapy with cardiovascular drugs while undergoing DAA treatment for hepatitis C. The clinicians' experience was combined with input from a qualified expert panel using a Consensus Delphi approach. The findings of this study offer essential and practical recommendations that can be readily applied in everyday clinical practice, helping physicians in managing hepatitis C virus patients undergoing DAA therapy.

Introduction

Antiviral treatments for hepatitis C virus (HCV) have transformed the disease's prognosis, allowing for better outcomes in complex patient populations, including older adults with multiple comorbidities. This shift has heightened awareness of drug interactions, particularly in patients treated with direct-acting antivirals (DAAs).

A recent retrospective study indicated that the most common comorbidities among HCV patients treated with DAAs include anxiety, hypertension, dyslipidemia, diabetes, chronic obstructive pulmonary disease, and depression.[1] In parallel, the most frequently co-prescribed medications are analgesics, antibiotics, anxiolytics, anti-

inflammatory drugs, antihypertensives, statins, and proton pump inhibitors.[1] International guidelines emphasize the need for a thorough evaluation of potential drug interactions before initiating HCV-targeted therapy,[2] with the Liverpool University database being the most widely used resource for this purpose.[3]

Among age-related comorbidities, hypertension, cardiovascular (CV) diseases, and metabolic disorders are particularly common. In patients treated with DAAs, dose modifications or drug substitutions occur more frequently for those on NS3/4 protease inhibitors (*e.g.*, glecaprevir/pibrentasvir) than for those on NS3/4-free regimens (*e.g.*, sofosbuvir/velpatasvir).[4] However, HCV infection is not yet listed as a CV risk factor in prevention guidelines, unlike inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease, psoriasis, and ankylosing spondylitis.[5] Interestingly, recent evidence suggests that DAA therapy can reduce the incidence of CV events in HCV patients post-treatment,[6] underscoring that DAAs should not be suspended or under-prescribed.

According to the Liverpool University database, diuretics and β-blockers generally do not exhibit significant interactions with DAAs.[3] However, calcium antagonists, particularly those affecting cytochrome P450 or inhibiting the renin-angiotensin-aldosterone system, may be affected by DAA-mediated inhibition of OATP1B1. Special caution is required with non-dihydropyridine calcium antagonists used for rate control in atrial fibrillation.

For anticoagulant therapy, vitamin K inhibitors are generally contraindicated in cases of hepatic impairment due to their metabolism. The Liverpool database highlights concerns about vitamin K inhibitors with complex metabolic profiles.[3] Acenocoumarol may be a safer alternative to warfarin in such patients. Novel oral anticoagulants (NOACs) like dabigatran, apixaban, and edoxaban, which are primarily renally excreted, exhibit fewer interactions with DAAs. However, DAA-mediated P-glycoprotein (P-gp) inhibition can significantly raise plasma NOAC levels, increasing the risk of bleeding. Data on these interactions remain limited.

Given the complexities outlined, this project was designed to assist clinical decision-making by clarifying DAA interactions with CV drugs and establishing therapeutic priorities for these challenging cases.[7] A multidisciplinary board – including experts in cardiology, internal medicine, gastroenterology, infectious diseases and diabetology – formed a broader expert panel (EP) of 30 members, who provided insights through two rounds of questionnaires following the Delphi methodology. The recommendations generated from this process are presented in this manuscript.

Materials and Methods

This project utilized the Delphi method, a well-established and validated consensus-building process frequently employed in health research and clinical decision-making.[8-11] The Delphi methodology is characterized by three core principles: anonymity, controlled feedback, and statistical group responses. These features make it a valuable tool for generating expert agreement on complex clinical challenges.[12]

The study was conducted from June to October 2023. The topics for discussion were developed into two questionnaires (*Supplementary Material – Questionnaires*) presented to a panel of clinicians representing various specialties, including cardiology, hematology, internal medicine, diabetology, infectious diseases, and gastroenterology. The first questionnaire (Q1) comprised 22 Likert scale questions,[13] where respondents rated their agreement from 1 (strong disagreement) to 9 (strong agreement). Six additional questions involved multiple-choice answers, and two further questions asked respondents to rank items by importance. The second questionnaire (Q2) consisted of 20 questions, again using a Likert scale for responses.

Demographic data

Before distributing the main survey, an advisory board of seven experts reviewed relevant literature and designed Q1. This included a demographic section where respondents provided details such as the type and size of their institutions, years of clinical experience, and geographic location. These demographic variables, such as age, years of experience, and field of expertise, were used as covariates in the statistical analysis. The survey also collected data on the healthcare centers involved, including the services they provided, patient management protocols, and levels of informatization.

The median age of the respondents was 61 years (range: 41-71), and their median work experience was 24 years (range: 6-44). Most participants specialized in hepatology (44%), followed by cardiology (24%) and infectiology (16%). The median experience in their respective fields was 19 years (range: 6-43). Detailed characteristics of the study population are shown in Table 1.

Following the analysis of Q1 results, the advisory board convened to discuss findings and design Q2. This was created to address ambiguous responses from Q1 and further evaluate specific diagnostic, therapeutic, and management procedures. Both Q1 and Q2 were administered through a digital platform to an EP recruited from 38 centers across the country, representing a multidisciplinary team of cardi-

Table 1. Characteristics of the study population.

	n=25
Age, years (median, min-max)	48.5, 35-70
Overall working experience, years (median, min-max)	24, 6-44
Field of prevalent activity	
Cardiology (n)	6
Hepatology (n)	11
Infectivology (n)	4
Experience in the field of prevalent activity, years (median, min-max)	19, 6-43

ologists, hematologists, internists, diabetologists, infectiologists, and gastroenterologists.

The study was conducted in two phases. In the first phase, Q1 was sent to the EP in June, and statistical analysis was performed on the 25 participants (66% of the initial cohort) who responded. In the second phase, Q2 was distributed in October to the same participants and statistical analyses were completed for 22 respondents (88% of Q1 respondents). The Q2 survey was designed to clarify topics where responses had been ambiguous in Q1.

Responses were analyzed as frequencies relative to the total number of respondents. Expert consensus was assessed using the RAND Corporation's Delphi method,[14] which employs a 1 to 9 Likert scale. The degree of consensus was quantified using the Inter-Percentile Range Adjusted for Symmetry method, which adjusts for score dispersion and panel symmetry to determine the appropriateness of each statement.

Statistical analysis

Statistical analysis was conducted using SPSS version 22.0 for Windows (IBM Corporation, Chicago, IL, USA). Data are presented as either mean ± standard deviation or frequency (percentage), depending on the variable type. Differences between categorical variables were assessed using the chi-square test (χ^2), while differences between continuous variables were evaluated using one-way analysis of variance. A p-value of less than 0.05 was considered statistically significant.

Results

Study population

A total of 38 experts were invited to participate in the project, with 25 responding to the Q1, and 22 completing both Q1 and the Q2. The median age of respondents was 61 years (range: 41-71). Detailed characteristics of the study participants are presented in Table 1.

Participants were asked to rate tools used to assess the risk of drug interactions before initiating HCV therapy. The University of Liverpool drug interaction database received the highest score (median = 9), followed by European Association for the Study of the Liver (EASL) recommendations (median = 8.5), personal experience (median = 7), medication leaflets (median = 5) and Medscape (median = 2).

The most common comorbidities reported among HCV patients were hypertension (68%), dyslipidemia (64%), diabetes (58%) and ischemic cardiopathy (54%). These conditions aligned with the most frequently prescribed medications, which included antihypertensives, lipid-lowering agents, antidiabetic drugs and antiplatelet agents.

Supplementary Table 1 and Figures 1 and 2 present the

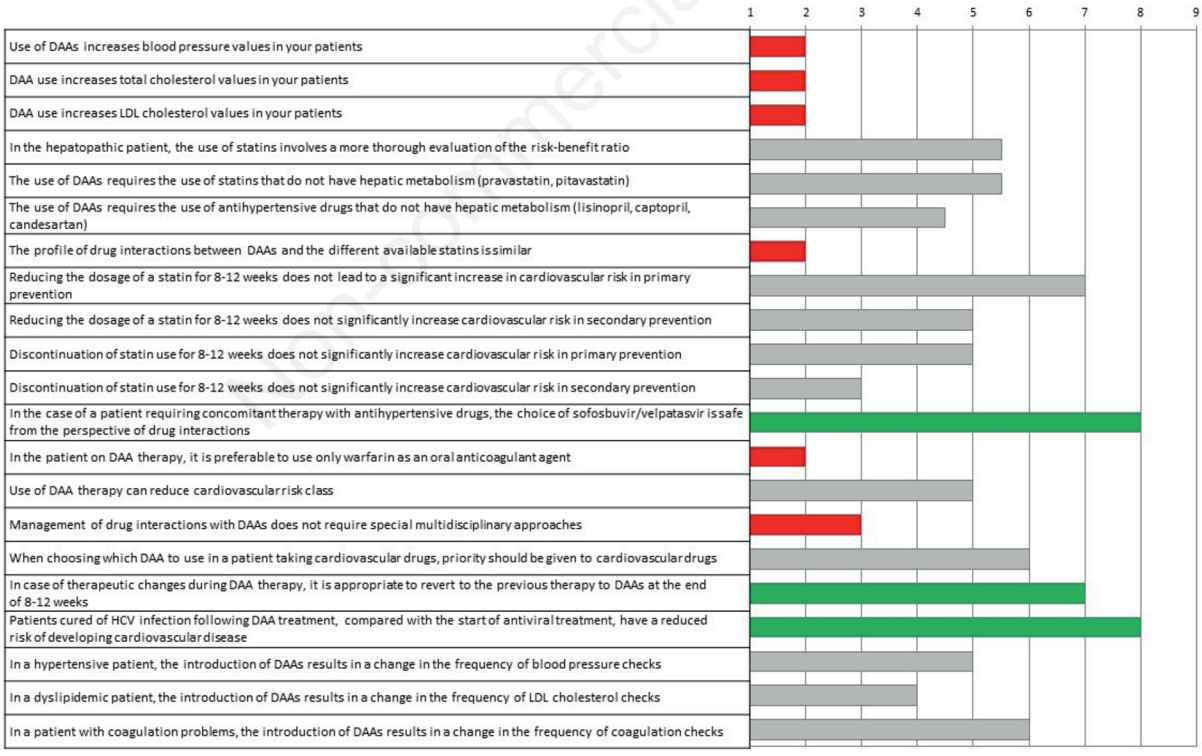

Figure 1. The appropriateness of the statements of Questionnaire 1 evaluated according to the RAND/UCLA method. Green bars: experts agree on the appropriateness of the proposed statement. Red bars: experts agree on the inappropriateness of the proposed statement. Gray bars: experts did not reach a consensus on the appropriateness or inappropriateness of the proposed statement. The evaluation of the statement "Reducing the dose of a statin for 8-12 weeks does not lead to a significant increase in cardiovascular risk in primary prevention," which received an average score of 7, was classified as "uncertain" due to greater variability among responders, as indicated by an IQR value of 5 (see *Supplementary Table 1*).

appropriateness indexes evaluated using the RAND/UCLA Method. In Q1, expert consensus confirmed the correctness or appropriateness of the following three statements: i) in patients requiring concomitant antihypertensive therapy, the combination of sofosbuvir/velpatasvir is safe regarding drug interactions; ii) if therapeutic changes occur during DAA therapy, it is advisable to revert to the previous DAA regimen after completing the 8-12 week course; iii) patients who achieve a cure following DAA therapy for HCV experience a reduced risk of developing cardiovascular disease compared to their baseline risk at the start of treatment.

Conversely, consensus was reached on the inappropriateness of seven statements: i) the use of DAAs increases blood pressure in patients; ii) the use of DAAs increases total cholesterol levels; iii) the use of DAAs increases low-density lipoprotein (LDL) cholesterol levels; iv) the drug interaction profile between DAAs and various statins is similar; v) discontinuing statins for 8-12 weeks does not significantly increase cardiovascular risk in patients undergoing secondary prevention; vi) warfarin should be the preferred oral anticoagulant in patients on DAA therapy; vii) managing drug interactions in DAA therapy does not require a multidisciplinary approach.

For the remaining twelve statements, consensus was not achieved, with median scores near 5 (neutral) or significant variability among raters.

After the results of Q1 were shared with the participants and revisions were made to unclear or ambiguous statements, Q2 was administered to the 25 participants who completed the first round. In some cases, the advisory board adjusted the phrasing from negative to positive. For example, the Q1 statement "Suspension of statin use for 8-12 weeks does not lead to a significant increase in cardiovascular risk in secondary prevention" was revised to "Suspension of statin use for 8-12 weeks leads to a significant increase in cardiovascular risk in secondary prevention" for Q2.

Among the 12 statements that failed to reach consensus in Q1, three achieved a consensus of being incorrect or inappropriate in Q2: i) when using DAAs, only antihypertensive drugs without hepatic metabolism (*e.g.*, lisinopril, captopril, candesartan) should be prescribed; ii) reducing the dose of a statin for 8-12 weeks significantly increases cardiovascular risk in primary prevention; iii) in patients with dyslipidemia, more frequent monitoring of LDL cholesterol levels is necessary during DAA treatment.

In one instance, consensus was reached on the appropriateness of the following statement: in patients on warfarin therapy, more frequent monitoring of coagulation parameters is necessary during DAA treatment.

For the remaining eight items, no consensus was achieved even in the second round. These unresolved items included questions about the CV risk associated with statin dose reduction during DAA therapy in primary and secondary prevention, the safety of glecaprevir/pibrentasvir in hypertensive patients, the role of DAA therapy in reducing CV risk, the prioritization of CV drugs when choosing a DAA regimen, and whether more frequent monitoring of blood pressure is needed during DAA treatment.

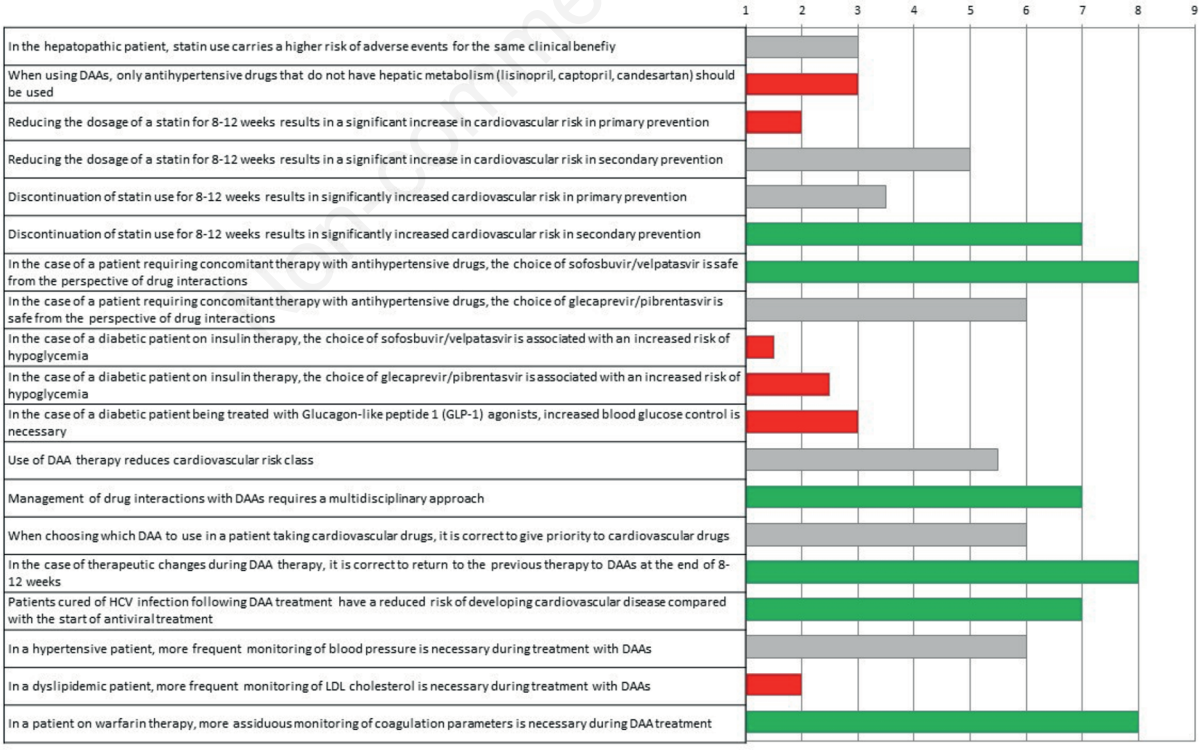

Figure 2. The appropriateness of the statements of Questionnaire 2 evaluated according to the RAND/UCLA method. Green bars: experts agree on the appropriateness of the proposed statement. Red bars: experts agree on the inappropriateness of the proposed statement. Gray bars: experts did not reach a consensus on the appropriateness or inappropriateness of the proposed statement.

Discussion

This Delphi project offers important insights to inform clinical decision-making about drug interactions between DAAs and CV medications in patients with hepatitis C. The recommendations span several critical areas, including: i) pre-treatment assessment; ii) selection of DAAs; iii) management of CV drugs in HCV patients on DAAs; iv) therapy modifications during DAA treatment; v) CV risk management.

The complexity of treating HCV patients with DAAs continues to evolve, especially as these patients tend to be older and often present with multiple comorbidities. Additionally, polypharmacy increases the likelihood of drug-drug interactions. Although tools like the University of Liverpool drug interaction database help clinicians navigate these interactions, practical, actionable guidelines are still lacking. This project was designed to fill this gap through expert consensus and provide clear take-home messages, which we can categorize by treatment phase and drug class.

Pre-treatment assessment

The University of Liverpool drug interaction database was rated the preferred tool for assessing drug interaction risk before initiating HCV treatment. This aligns with previous literature.[4,15] EASL recommendations were also endorsed as a valuable resource, though the Liverpool database was rated more highly by the panel.

Choice of direct-acting antivirals

Based on the expert consensus, sofosbuvir/velpatasvir was identified as a safe and preferable regimen for patients on concomitant antihypertensive therapy. This finding is consistent with real-world data,[4] which suggests that sofosbuvir/velpatasvir is frequently prescribed for older, comorbid patients because it requires fewer dose adjustments or therapy interruptions compared to other regimens, such as those containing NS3/4 inhibitors (*e.g.*, glecaprevir/pibrentasvir).

Treatment changes/adjustments during direct-acting antiviral therapy

Antihypertensive therapy often requires modification during DAA treatment, but these adjustments should be limited to the treatment window. Recent data from 414 patients aged over 65 years with HCV treated with DAAs showed that statins were frequently discontinued and antihypertensives were often adjusted during treatment.[1] This approach of "deprescribing" resulted in a stable reduction in the number of medications taken, improving patients' quality of life. DAAs have been shown to be effective regardless of disease severity, comorbidities, or age, and their use should not be restricted based on polypharmacy concerns.

Cardiovascular risk management and reduction in patients with hepatitis C virus

Recent research involving 280 patients who achieved sustained virologic response following DAA therapy demonstrated a reduction in liver fibrosis and improvements in liver function. An observational study found that antiviral therapy was associated with a reduction in glomerular filtration rate and LDL cholesterol, although other parameters (*e.g.*, uric acid, fasting blood glucose, and hemoglobin) showed mixed results.[16] Therefore, therapeutic adjustments may be required during DAA therapy.

The consensus reached by this panel suggests the following key points: i) curing HCV with DAAs significantly reduces the risk of CV disease, and thus, DAA therapy should not be suspended in patients with a high CV risk profile; ii) DAA treatment does not inherently worsen CV risk or complicate the management of CV comorbidities; iii) DAAs do not elevate blood pressure, total cholesterol or LDL cholesterol levels in HCV patients; iv) the interaction profile between DAAs and statins varies by drug, meaning not all statins require adjustment.[16]

Drug-specific considerations

For anticoagulant therapy, warfarin is generally not recommended for HCV patients on DAAs, but if it must be used, close monitoring is required. NOACs such as dabigatran, edoxaban, apixaban, and rivaroxaban are safer alternatives due to their minimal hepatic metabolism. However, interactions with P-gp inhibitors can elevate NOAC plasma levels, increasing bleeding risk and thus require careful monitoring. Acenocoumarol may be a safer alternative for patients requiring anticoagulation.[3]

In the case of antihypertensive therapy, it is not necessary to limit treatment to drugs without hepatic metabolism (*e.g.*, lisinopril, captopril, candesartan), contrary to earlier concerns. Reducing statin dosage for 8-12 weeks does not significantly increase CV risk in patients under primary prevention, although more frequent LDL cholesterol monitoring may be advisable in patients with dyslipidemia on DAA therapy.

Multidisciplinary approach

A major conclusion of this project is the necessity for a multidisciplinary approach to managing HCV patients treated with DAAs. The complexity of drug interactions and the frequent presence of comorbidities necessitate collaborative care involving multiple specialties. Cardiologists, hepatologists, internists, gastroenterologists, and diabetologists must work together to optimize outcomes and ensure patient safety. This collaborative approach has been successfully implemented in more complex scenarios, such as HCV-HIV co-infection, and should be adopted more broadly for HCV patients with CV comorbidities.[17]

Conclusions

This Delphi project provides essential, practical recommendations that can be readily applied in daily clinical practice to manage HCV patients receiving DAAs, particularly those with CV comorbidities. The study underscores the need for a multidisciplinary approach, as no single specialist can fully address the complex treatment demands of this population.

Key findings from this project offer valuable insights into the interactions between DAAs and commonly prescribed CV drugs. These include the importance of conducting comprehensive pre-treatment assessments using resources such as the

University of Liverpool drug interaction database, alongside the EASL guidelines, to guide therapeutic decisions.

Sofosbuvir/velpatasvir was identified as the preferred regimen for patients requiring concomitant antihypertensive therapy due to its favorable interaction profile. Furthermore, the study highlights that modifications to antihypertensive or statin therapy during DAA treatment should be confined to the treatment period and should not be extended beyond it.

One of the most significant conclusions from this study is that successful treatment of HCV with DAAs markedly reduces CV risk, supporting the aggressive management of HCV infection even in patients with high CV risk. Concerns about potential drug interactions or polypharmacy should not lead to delays or under-prescription of DAA therapy, as these patients benefit not only from viral eradication but also from a reduction in CV events.[4]

The study also clarifies that not all statins or antihypertensives need to be discontinued or reduced during DAA therapy. While close monitoring of statin interactions is critical in high-risk patients, discontinuing or reducing statins does not necessarily increase CV risk in those undergoing primary prevention. However, in secondary prevention patients, reducing statin use for 8-12 weeks may significantly elevate CV risk, necessitating careful monitoring and individualized therapy.[4]

Finally, this project emphasizes the growing complexity of treating older, comorbid HCV patients, given the increasing number of concomitant medications and the risk of drug interactions. The insights from this Delphi study aim to fill existing gaps in clinical guidelines and provide practical recommendations for clinicians. However, optimal management of HCV patients on DAA therapy, particularly those with cardiovascular conditions, requires a coordinated, multidisciplinary approach, involving specialists across various fields to ensure the best outcomes.[16]

It is important to acknowledge the study's limitations. Some of the drugs included in the questionnaire, such as pitavastatin, are not widely available in Italy, which could have limited the respondents' ability to provide accurate feedback on these medications. Furthermore, some of the referenced drugs may not be the only ones with similar metabolic pathways, meaning that the findings could apply to other drugs not explicitly mentioned (*e.g.*, perindopril as a representative of ACE inhibitors). Despite these limitations, the study offers a strong framework for addressing drug interactions in HCV patients treated with DAAs, especially those with cardiovascular comorbidities.

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Online supplementary material:

Supplementary Table 1. Indexes of appropriateness evaluated according to the RAND/UCLA method.

Supplementary Material – Questionnaires. Delphi questionnaire 1 and Delphi questionnaire 2.