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SUPPLEMENTARY MATERIAL

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

Ivan Gentile,[1] Giancarlo Agnelli,[2] Angelo Avogaro,[3] Claudio Borghi,[4] Alessia Ciancio,[5] Ernesto Claar,[6] Patrizio Pasqualetti,[7] Pasquale Perrone Filardi[8]

[1]Department of Clinical Medicine and Surgery, Federico II University of Naples; [2]Internal, Vascular and Emergency Medicine-Stroke Unit, University of Perugia; [3]Section of Diabetes and Metabolic Diseases, Department of Medicine, University of Padua; [4]Internal Medicine, Department of Medical and Surgical Sciences, Policlinic S. Orsola-Malpighi, University of Bologna; [5]Gastroenterology Unit, Department of Internal Medicine, Città della Salute e della Scienza di Torino, University of Turin; [6]Liver Unit, Ospedale Evangelico Betania, Naples; [7]Section of Health Statistics and Biometry, Department of Public Health and Infectious Diseases, Faculty of Pharmacy and Medicine, Sapienza University of Rome; [8]Department of Advanced Biomedical Sciences, Federico II University of Naples Italy

Correspondence: Patrizio Pasqualetti, Section of Health Statistics and Biometry, Department of Public Health and Infectious Diseases, Faculty of Pharmacy and Medicine, Sapienza University of Rome, Rome, Italy.
Tel.: +39 06 4991 4294.
E-mail: patrizio.pasqualetti@uniroma1.it

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

Questionnaire	Item	Question		median	IQR	IPRAS	evaluation	Questionnaire	Item	Question	median	IQR	IPRAS	evaluation
q1	q1_d01_r1	What tool do you use to assess the risk of drug interactions before starting HCV therapy?	EASL 2020 Recommendations	8,5	2,75	7,075	appropriate							
q1	q1_d01_r2		University of Liverpool database	9	1	8,35	appropriate							
q1	q1_d01_r3		Fact sheet	5	5	4,6	uncertain							
q1	q1_d01_r4		Personal experience	7	3	5,35	appropriate							
q1	q1_d01_r5		Medscape	2	3	6,1	inappropriate							
q1	q1_d04_r1	Use of DAAs increases blood pressure values in your patients		2	2	6,85	inappropriate							
q1	q1_d05_r1	DAA use increases total cholesterol values in your patients		2	4	5,35	inappropriate							
q1	q1_d06_r1	DAA use increases LDL cholesterol values in your patients		2	3,5	5,35	inappropriate							
q1	q1_d07_r1	In the hepatopathic patient, the use of statins involves a more thorough evaluation of the risk-benefit ratio		5,5	4,75	2,35	uncertain	q2	q2_d07_r1	In the hepatopathic patient, statin use carries a higher risk of adverse events for the same clinical benefit	3	5,75	4,375	uncertain
q1	q1_d08_r1	The use of DAAs requires the use of statins that do not have hepatic metabolism (pravastatin, pitavastatin)		5,5	4,75	3,85	uncertain							
q1	q1_d09_r1	The use of DAAs requires the use of antihypertensive drugs that do not have hepatic metabolism (lisinopril, captopril, candesartan)		4,5	4	3,475	uncertain	q2	q2_d09_r1	When using DAAs, only antihypertensive drugs that do not have hepatic metabolism (lisinopril, captopril, candesartan) should be used	3	3,75	4,6	inappropriate

q1	q1_d13_r1	The profile of drug interactions between DAAs and the different available statins is similar	2	4	6,1	inappropriate							
q1	q1_d14_r1	Reducing the dosage of a statin for 8-12 weeks does not lead to a significant increase in cardiovascular risk in primary prevention	7	5	3,85	uncertain	q2	q2_d14_r1	Reducing the dosage of a statin for 8-12 weeks results in a significant increase in cardiovascular risk in primary prevention	2	4	5,575	inappropriate
q1	q1_d15_r1	Reducing the dosage of a statin for 8-12 weeks does not significantly increase cardiovascular risk in secondary prevention	5	4	3,25	uncertain	q2	q2_d15_r1	Reducing the dosage of a statin for 8-12 weeks results in a significant increase in cardiovascular risk in secondary prevention	5	3,75	2,875	uncertain
q1	q1_d16_r1	Discontinuation of statin use for 8-12 weeks does not significantly increase cardiovascular risk in primary prevention	5	5	3,25	uncertain	q2	q2_d16_r1	Discontinuation of statin use for 8-12 weeks results in significantly increased cardiovascular risk in primary prevention	3,5	3,75	4,375	uncertain
q1	q1_d17_r1	Discontinuation of statin use for 8-12 weeks does not significantly increase cardiovascular risk in secondary prevention	3	4	5,35	inappropriate	q2	q2_d17_r1	Discontinuation of statin use for 8-12 weeks results in significantly increased cardiovascular risk in secondary prevention	7	3	4,825	appropriate
q1	q1_d20_r1	In the case of a patient requiring concomitant therapy with antihypertensive drugs, the choice of sofosbuvir/velpatasvir is safe from the perspective of drug interactions	8	2	6,1	appropriate	q2	q2_d20a_r1	In the case of a patient requiring concomitant therapy with antihypertensive drugs, the choice of sofosbuvir/velpatasvir is safe from the perspective of drug interactions	8	2	6,625	appropriate

							q2	q2_d20b_r1	In the case of a patient requiring concomitant therapy with antihypertensive drugs, the choice of glecaprevir/pibrentasvir is safe from the perspective of drug interactions	6	2	3,85	uncertain
							q2	q2_d20c_r1	In the case of a diabetic patient on insulin therapy, the choice of sofosbuvir/velpatasvir is associated with an increased risk of hypoglycaemia	1,5	3,75	6,1	inappropriate
							q2	q2_d20d_r1	In the case of a diabetic patient on insulin therapy, the choice of glecaprevir/pibrentasvir is associated with an increased risk of hypoglycaemia	2,5	3,75	6,1	inappropriate
							q2	q2_d20e_r1	In the case of a diabetic patient being treated with Glucagon-like peptide 1 (GLP-1) agonists, increased blood glucose control is necessary	3	4	5,575	inappropriate
q1	q1_d21_r1	In the patient on DAA therapy, it is preferable to use only warfarin as an oral anticoagulant agent	2	4	5,2	inappropriate							
q1	q1_d23_r1	Use of DAA therapy can reduce cardiovascular risk class	5	4	2,5	uncertain	q2	q2_d23_r1	Use of DAA therapy reduces cardiovascular risk class	5,5	3,5	3,85	uncertain

q1	q1_d24_r1	Management of drug interactions with DAAs does not require special multidisciplinary approaches	3	5	5,35	inappropriate	q2	q2_d24_r1	Management of drug interactions with DAAs requires a multidisciplinary approach	7	3	4,825	appropriate
q1	q1_d25_r1	When choosing which DAA to use in a patient taking cardiovascular drugs, priority should be given to cardiovascular drugs	6	3	3,85	uncertain	q2	q2_d25_r1	When choosing which DAA to use in a patient taking cardiovascular drugs, it is correct to give priority to cardiovascular drugs	6	3	4,375	uncertain
q1	q1_d26_r1	In case of therapeutic changes during DAA therapy, it is appropriate to revert to the previous therapy to DAAs at the end of 8-12 weeks	7	3	5,35	appropriate	q2	q2_d26_r1	In the case of therapeutic changes during DAA therapy, it is correct to return to the previous therapy to DAAs at the end of 8-12 weeks	8	3,5	6,85	appropriate
q1	q1_d27_r1	Patients cured of HCV infection following DAA treatment, compared with the start of antiviral treatment, have a reduced risk of developing cardiovascular disease	8	2	5,35	appropriate	q2	q2_d27_r1	Patients cured of HCV infection following DAA treatment have a reduced risk of developing cardiovascular disease compared with the start of antiviral treatment	7	2	5,575	appropriate
q1	q1_d28_r1	In a hypertensive patient, the introduction of DAAs results in a change in the frequency of blood pressure checks	5	5	2,95	uncertain	q2	q2_d28_r1	In a hypertensive patient, more frequent monitoring of blood pressure is necessary during treatment with DAAs	6	5	3,325	uncertain
q1	q1_d29_r1	In a dyslipidemic patient, the introduction of DAAs results in a change in the frequency of LDL cholesterol checks	4	4	4,6	uncertain	q2	q2_d29_r1	In a dyslipidemic patient, more frequent monitoring of LDL cholesterol is necessary during treatment with DAAs	2	4,5	6,325	inappropriate
q1	q1_d30_r1	In a patient with coagulation problems, the introduction of DAAs results in a change in the frequency of coagulation checks	6	4	3,85	uncertain	q2	q2_d30_r1	In a patient on warfarin therapy, more assiduous monitoring of coagulation parameters is necessary during DAA treatment	8	3	5,875	appropriate

Supplementary Material - Questionnaires

DELPHI QUESTIONNAIRE 1

1. **Which tool do you use to assess the risk of drug interactions before starting HCV therapy?**
[express the level of implementation for each response option by selecting a score between 1 (lowest grade) and 9 (highest grade)]
   a. EASL 2020 recommendations
   b. University of Liverpool database
   c. Package insert
   d. Personal experience
   e. Medscape
   f. Not assessable (physician not prescribing HCV therapy)

2. **Out of 10 of your patients with hepatitis C, how many have the following comorbidities?**
[express a percentage on a scale of 0 to 10]
   a. COPD
   b. Ischemic heart disease
   c. Depression
   d. Diabetes
   e. Dyslipidaemia
   f. Epilepsy
   g. Atrial fibrillation
   h. Renal failure
   i. Arterial hypertension
   j. Thyroid disease
   k. Parkinson's disease
   l. Other (specify)

3. **What are the most frequent chronic therapies among your HCV patients treated with DAAs?**
[maximum of 6 answers can be selected]
   a. Analgesics/NSAIDs
   b. Anxiolytics / Antidepressants
   c. Antacids
   d. Antiplatelet
   e. Antiarrhythmics
   f. Antiepileptics
   g. Antihypertensives
   h. Chemotherapy
   i. Proton pump inhibitors
   j. NAO
   k. Statins
   l. Warfarin
   m. Antidiabetics
   n. Other (specify)

4. **The use of DAAs increases blood pressure values in your patients.**
[indicate your level of agreement with this statement by selecting a score between 1 (complete disagreement) and 9 (maximum agreement)]

5. **The use of DAAs increases total cholesterol values in his patients.**
[indicate your level of agreement with this statement by selecting a score between 1 (complete disagreement) and 9 (maximum agreement)]

6. **The use of DAAs increases LDL cholesterol values in his patients.**
[indicate your level of agreement with this statement by selecting a score between 1 (complete disagreement) and 9 (maximum agreement)]

7. **In the hepatopathic patient, the use of statins involves a more thorough evaluation of the risk-benefit ratio.**
[indicate your level of agreement with this statement by selecting a score between 1 (complete disagreement) and 9 (maximum agreement)]

8. **The use of DAAs requires the use of statins that do not have hepatic metabolism (pravastatin, pitavastatin).**
[indicate your level of agreement with this statement by selecting a score between 1 (complete disagreement) and 9 (maximum agreement)]

9. **The use of DAAs requires the use of antihypertensive drugs that do not have hepatic metabolism (lisinopril, captopril, candesartan).**
[indicate your level of agreement with this statement by selecting a score between 1 (complete disagreement) and 9 (maximum agreement)]

10. **Which cardiovascular drug do you consider a priority not to discontinue in a patient on DAA therapy?**
[indicate the order of importance you assign to the proposed items by giving value 1 to the priority sequence and value 5 to the lower priority sequence]
   a. Statins/hypolipidemic drugs
   b. NOACs/Anticoagulants
   c. Antihypertensives
   d. All
   e. All, at a reduced dosage

11. **Which class of cardiovascular drugs is most likely to have drug interactions during DAA therapy?**
[indicate the order of importance you assign to the proposed items by giving value 1 to the priority sequence and value 4 to the lower priority sequence]
   a. Statins/hypolipidemic drugs
   b. NOACs/Anticoagulants
   c. Antihypertensives
   d. All

12. **In case of drug interaction between DAA and antihypertensive drug, would you opt for:**
[only one response can be selected]
○ the discontinuation of the antihypertensive during DAA therapy (8-12 weeks)
○ the replacement of the antihypertensive during DAA therapy (8-12 weeks)
○ the change in antihypertensive dosage during DAA therapy (8-12 weeks)
○ the choice of a different DAA (8-12 weeks)

13. **The profile of drug interactions between DAAs and the different available statins is similar.**
[indicate your level of agreement with this statement by selecting a score between 1 (complete disagreement) and 9 (maximum agreement)]

14. **Reducing the dosage of a statin for 8-12 weeks does not significantly increase cardiovascular risk in primary prevention.**
[indicate your level of agreement with this statement by selecting a score between 1 (complete disagreement) and 9 (maximum agreement)]

15. **Reducing the dosage of a statin for 8-12 weeks does not significantly increase cardiovascular risk in secondary prevention.**
[indicate your level of agreement with this statement by selecting a score between 1 (complete disagreement) and 9 (maximum agreement)]

16. **Stopping statin use for 8-12 weeks does not significantly increase cardiovascular risk in primary prevention.**
[indicate your level of agreement with this statement by selecting a score between 1 (complete disagreement) and 9 (maximum agreement)]

17. **Stopping statin use for 8-12 weeks does not significantly increase cardiovascular risk in secondary prevention.**
[indicate your level of agreement with this statement by selecting a score between 1 (complete disagreement) and 9 (maximum agreement)]

18. **In case of drug interaction between DAAs and statins, would opt for:**
[only one response can be selected]
○ the discontinuation of statins during DAA therapy (8-12 weeks)
○ the replacement of statins with hypolipidemic drugs or a non-statin hypolipidemic drug (8-12 weeks)
○ the choice of a different DAA (8-12 weeks)

19. **In case of drug interaction between DAAs and NOACs, would opt for:**
[only one response can be selected]
○ the discontinuation of NOACs during DAA therapy (8-12 weeks)
○ the replacement of NOACs with a different anticoagulant therapy (8-12 weeks)
○ the choice of a different DAA (8-12 weeks)

20. **In the case of a patient requiring concomitant therapy with antihypertensive drugs, the choice of sofosbuvir/velpatasvir is safe from the perspective of drug interactions.**
[indicate your level of agreement with this statement by selecting a score between 1 (complete disagreement) and 9 (maximum agreement)]

21. **In the patient on DAA therapy, it is preferable to use only warfarin as an oral anticoagulant agent.**
[indicate your level of agreement with this statement by selecting a score between 1 (complete disagreement) and 9 (maximum agreement)]

22. **In case of polypharmacotherapy in the patient being treated with DAAs, would opt for:**
[only one response can be selected]
○ not changing the total doses of the current drug
○ choosing the antiviral with the least interference
○ replacing the current medication

23. **The use of DAA therapy can reduce cardiovascular risk class.**
[indicate your level of agreement with this statement by selecting a score between 1 (complete disagreement) and 9 (maximum agreement)]

24. **The management of drug interactions with DAAs does not require particular multidisciplinary approaches.**
[indicate your level of agreement with this statement by selecting a score between 1 (complete disagreement) and 9 (maximum agreement)]

25. **When choosing which DAA to use in a patient taking cardiovascular drugs, priority should be given to cardiovascular medications.**
[indicate your level of agreement with this statement by selecting a score between 1 (complete disagreement) and 9 (maximum agreement)]

26. **In case of therapeutic changes during DAA therapy, it is appropriate to return to the previous treatment to DAAs at the end of 8-12 weeks.**
[indicate your level of agreement with this statement by selecting a score between 1 (complete disagreement) and 9 (maximum agreement)]

27. **Compared with the start of antiviral treatment, patients cured of HCV infection following DAA treatment have a reduced risk of developing cardiovascular disease.**
[indicate your level of agreement with this statement by selecting a score between 1 (complete disagreement) and 9 (maximum agreement)]

28. **In a hypertensive patient, the introduction of DAAs results in a change in the frequency of blood pressure checks.**
[indicate your level of agreement with this statement by selecting a score between 1 (complete disagreement) and 9 (maximum agreement)]

29. **In a dyslipidemic patient, the introduction of DAAs results in a change in the frequency of LDL cholesterol checks.**
[indicate your level of agreement with this statement by selecting a score between 1 (complete disagreement) and 9 (maximum agreement)]

30. **In a patient with coagulation problems, the introduction of DAAs results in a change in the frequency of coagulation checks.**
[indicate your level of agreement with this statement by selecting a score between 1 (complete disagreement) and 9 (maximum agreement)]

DELPHI QUESTIONNAIRE 2

7. **In the hepatopathic patient, statin use carries a higher risk of adverse events for the same clinical benefit.**
[indicate your level of agreement with this statement by selecting a score between 1 (complete disagreement) and 9 (maximum agreement)]

9. **Only antihypertensive drugs that do not have hepatic metabolism (lisinopril, captopril, candesartan) should be used when using DAAs.**
[indicate your level of agreement with this statement by selecting a score between 1 (complete disagreement) and 9 (maximum agreement)]

14. **<u>Dose reduction</u> of a statin for 8-12 weeks results in a significant increase in cardiovascular risk in primary prevention.**
[indicate your level of agreement with this statement by selecting a score between 1 (complete disagreement) and 9 (maximum agreement)]

15. **<u>Dose reduction</u> of a statin for 8-12 weeks results in a significant increase in cardiovascular risk in secondary prevention.**
[indicate your level of agreement with this statement by selecting a score between 1 (complete disagreement) and 9 (maximum agreement)]

16. **<u>Discontinuation</u> of statin use for 8-12 weeks results in a significant increase in cardiovascular risk in primary prevention.**
[indicate your level of agreement with this statement by selecting a score between 1 (complete disagreement) and 9 (maximum agreement)]

17. **<u>Discontinuation</u> of statin use for 8-12 weeks results in significantly increased cardiovascular risk in secondary prevention.**
[indicate your level of agreement with this statement by selecting a score between 1 (complete disagreement) and 9 (maximum agreement)]

20.a. **In the case of a patient requiring concomitant therapy with antihypertensive drugs, the choice of sofosbuvir/velpatasvir is safe from the perspective of drug interactions.**
[indicate your level of agreement with this statement by selecting a score between 1 (complete disagreement) and 9 (maximum agreement)]

20.b. **In the case of a patient requiring concomitant therapy with antihypertensive drugs, the choice of glecaprevir/pibrentasvir is safe from the perspective of drug interactions.**
[indicate your level of agreement with this statement by selecting a score between 1 (complete disagreement) and 9 (maximum agreement)]

20.c. **In the case of a diabetic patient on insulin therapy, the choice of sofosbuvir/velpatasvir is associated with an increased risk of hypoglycemia.**
[indicate your level of agreement with this statement by selecting a score between 1 (complete disagreement) and 9 (maximum agreement)]

20.d. **In the case of a diabetic patient on insulin therapy, the choice of glecaprevir/pibrentasvir is associated with an increased risk of hypoglycemia.**
[indicate your level of agreement with this statement by selecting a score between 1 (complete disagreement) and 9 (maximum agreement)]

20.e. **In the case of a diabetic patient being treated with Glucagon-like peptide 1 (GLP-1) agonists, more blood glucose control is required.**
[indicate your level of agreement with this statement by selecting a score between 1 (complete disagreement) and 9 (maximum agreement)]

23. **Use of DAA therapy reduces cardiovascular risk class.**
[indicate your level of agreement with this statement by selecting a score between 1 (complete disagreement) and 9 (maximum agreement)]

24. **Management of drug interactions with DAAs requires a multidisciplinary approach.**
[indicate your level of agreement with this statement by selecting a score between 1 (complete disagreement) and 9 (maximum agreement)]

25. **When choosing which DAA to use in a patient taking cardiovascular drugs, prioritizing cardiovascular drugs is correct.**
[indicate your level of agreement with this statement by selecting a score between 1 (complete disagreement) and 9 (maximum agreement)]

26. **In case of therapeutic changes during DAA therapy, it is correct to return to the previous treatment to DAAs at the end of 8-12 weeks.**
[indicate your level of agreement with this statement by selecting a score between 1 (complete disagreement) and 9 (maximum agreement)]

27. **Patients cured of HCV infection following treatment with DAA have a reduced risk of developing cardiovascular disease compared with the start of antiviral therapy.**
[indicate your level of agreement with this statement by selecting a score between 1 (complete disagreement) and 9 (maximum agreement)]

28. **In hypertensive patients, more frequent monitoring of blood pressure is necessary during treatment with DAAs.**
[indicate your level of agreement with this statement by selecting a score between 1 (complete disagreement) and 9 (maximum agreement)]

29. **In a dyslipidemic patient, more frequent monitoring of LDL cholesterol is necessary during treatment with DAAs.**
[indicate your level of agreement with this statement by selecting a score between 1 (complete disagreement) and 9 (maximum agreement)]

30. **In a patient on warfarin therapy, more assiduous monitoring of coagulation parameters is necessary during DAA treatment.**
[indicate your level of agreement with this statement by selecting a score between 1 (complete disagreement) and 9 (maximum agreement)]