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Practical Suggestions for an Optimal Management of Vitamin K Antagonists: Italian Federation of Centers for the Diagnosis of Thrombotic Disorders and the Surveillance of the Antithrombotic Therapies (FCSA) Position Paper

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Thromb Haemost

Abstract

In the era of direct oral anticoagulants, vitamin K antagonists retain a clinically relevant role in thrombotic disorders. In Italy, approximately 20% of the patients on anticoagulant therapies receives a VKA, in most cases warfarin. The optimal management of this drug is challenging and cannot disregard its intricate and unpredictable pharmacokinetic properties and patient's thrombotic and bleeding risk. Several clinical issues encountered during warfarin treatment are still unanswered and are tentatively addressed by physicians. In this regard, the Italian Federation of Centers for the diagnosis of thrombotic disorders and the Surveillance of the Antithrombotic therapies (FCSA) provides some experience-based good clinical practice's suggestions on the following topics: (1) how to start the anticoagulant treatment with warfarin and warfarin induction regimen; (2) how to manage a subtherapeutic INR value; (3) how to manage a supratherapeutic INR value in asymptomatic patients; and (4) how to manage the association of warfarin with interfering drugs.

Keywords
- anticoagulant
- warfarin
- vitamin K antagonists

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Introduction

In the direct oral anticoagulant (DOACs) era, vitamin K antagonists (VKAs) still have a clinically relevant role in thrombotic disorders: VKAs are the only recommended anticoagulant drugs in several conditions with high thrombotic risk, such as valvular atrial fibrillation, mechanical heart valves, and antiphospholipid antibody syndrome. Among VKAs, warfarin is the most widely used and is within the list of the top 100 most prescribed drugs, for a total of more than 11,000,000 prescriptions in 2020 in the United States.[1]

The intricate properties of VKAs and their unpredictable pharmacokinetics make their handling challenging. Despite its long history of more than eight decades, warfarin is numbered among the most common causes of emergency hospitalization for adverse drug events, especially in older patients.[2] For the appropriate management of VKA treatment, the long half-life of the drug, the different half-life of vitamin K-dependent proteins, the assessment of patient's thrombotic and bleeding risk, and the great number of interfering factors should be taken into consideration. In this complex scenario, the international normalized ratio (INR) is the reference laboratory test for monitoring and optimizing the effectiveness and safety of anticoagulation with VKAs. However, several clinical issues encountered during VKA treatment are still tentatively addressed by physicians, given the lack of high-quality evidence. In this context, knowledge sharing, education programs, and experts' opinions have been essential tools to improve the quality of VKA treatment over the years. As a proof of this, it has been shown that in highly experience anticoagulation clinics, we can obtain higher values of time-in-therapeutic range (TTR) than those reported in many randomized clinical trials.[3,4]

On the basis of the experience gained, the Italian Federation of Centers for the diagnosis of thrombotic disorders and the Surveillance of the Antithrombotic therapies (FCSA) attempts to supplement the available guidelines[5] by providing a specific practical guidance addressing the following unmet clinical needs of the most worldwide used VKA, i.e., warfarin: *(1) how to start the anticoagulant treatment with warfarin and warfarin induction regimen; (2) how to manage a subtherapeutic INR value in asymptomatic patients; (3) how to manage a supratherapeutic INR value in asymptomatic patients; (4) how to manage the association of warfarin with interfering drugs.*

It is hereby specified that the following practical guidance cannot be directly transferred to the management of the other VKAs (i.e., acenocoumarol and phenprocoumon) as they have different half-lives and pharmacokinetic characteristics from warfarin.

FCSA Good Clinical Practice's Suggestions

How to Start the Anticoagulation with Warfarin and Warfarin Induction Regimen

Before starting warfarin, it is mandatory to check for hemoglobin, platelet count, liver function, creatinine, prothrombin time, and activated partial thromboplastin time and assess the absolute thromboembolic risk for the indication to treatment, as well as the patient's individual thrombotic and bleeding risk.

Educational Program

All patients who start warfarin treatment should be offered an appropriate educational program by the treating physician. Patients should be responsible of their own treatment and participate actively to it, to obtain the better quality and minimize adverse events. Patients should be well-informed that:

- The daily treatment scheme of warfarin is prescribed in a written form to properly check the current and past dose adjustments and the next INR control. Patients should receive an electronic or simple paper calendar to record INR values, date of the laboratory test, and daily dosage. Patients should receive a card indicating the anticoagulant treatment on board, with the aim to inform health professionals in case of trauma or access to emergency departments.
- Therapy should be regularly taken once daily, choosing preferably the late evening hours for the assumption, to allow the eventual prompt correction of dosing according to INR result.
- Clinical evidence[6] and the large experience in treating patients on VKA in the frame of FCSA centers suggest to avoid dietary restrictions. Patients should be encouraged to follow a free regular diet, even if VKA treatment has been usually associated with the need for very strict dietary indications, particularly in relation to vegetable intake. Indeed, the indication to follow a strict diet is only based on the mechanism of action of these drugs and not on solid clinical evidence. Patients should be instructed to report any important change in their dietary habits (i.e., hypocaloric or vegetarian diet to lose weight) and vitamin K intake for its possible effect on anticoagulation response of VKA. Patients should be informed that also large amounts of some dietary supplements, alcohol, and herbs can cause fluctuations in INR value by metabolic interference with cytochrome CYP3A4 and P-glycoprotein.[7]
- In case of intercurrent illness, patients should anticipate the scheduled INR control, particularly when over-anticoagulation is possible, such as in case of diarrhea or severe reduction of regular feeding. Supratherapeutic INRs are also frequently found in patients with heart failure, therefore INR checking is advised in case of increase of peripheral edema or worsening of dyspnea.
- In case of use of possible interfering drugs, patients should anticipate the scheduled INR control. They should avoid aspirin, when not specifically prescribed, and limit the use of nonsteroidal anti-inflammatory drugs to avoid the possible increase of the bleeding risk.
- It is advisable to regularly check of urine and stools to immediately identify mucosal bleeding events. In case of the occurrence of minor bleedings such as spontaneous

ecchymosis, gum bleeding, or epistaxis, INR check is also suggested. In case of epistaxis, blood pressure control is also recommended.
- Women of childbearing age should be accurately informed about the teratogenic effects of warfarin. In case of pregnancy, immediate warfarin stopping is warranted.
- The potential heavy bleeding associated with VKA should be discussed with premenopausal women at the beginning of anticoagulant treatment. Women should be taught how to quantify menstrual bleeding. In case of heavy menstrual bleeding, it is advisable a periodically monitoring of hemoglobin and iron supplements during menstrual flow.

Warfarin Induction Phase

Warfarin dose and INR checking: FCSA suggests different warfarin induction doses and INR checking according to patient's characteristics:

- *In stable patients*: start warfarin with a 5 mg daily loading dose for the first 4 days, then check the INR value on day 5 and adjust the dose accordingly by scheduling the next INR checking 4 to 6 days apart for the first 2 weeks. Thereafter, INR checking is recommended 1 week apart until its stabilization into the therapeutic range, then once every 3 to 4 weeks (maximum 6 weeks). By using this approach, the actual weekly warfarin maintenance dose can be predicted after the first 4 days of 5 mg loading dose, according to a specific published algorithm.[6]
- *In very elderly patients (i.e., >80 years old)*: start warfarin with 5 mg daily loading dose for the first 3 days, then check the INR value on day 4 and adjust the maintenance dose accordingly by scheduling the next INR checking and prescription 3 to 4 days apart for the first week. Thereafter, INR checking is recommended 1 week apart until its stabilization into the therapeutic range for three times. Then, INR checking can be scheduled once every 3 to 4 weeks.
- *In patients with congestive heart failure, liver disease, at high bleeding risk, or receiving amiodarone treatment (or other drugs known to increase the INR)*: it may be appropriate to start warfarin with 2.5 mg daily loading dose for the first 3 days.
- *In children*: start warfarin with a 0.2 mg/kg daily loading dose for the first 2 days, then check the INR value on day 3 and adjust the following dose accordingly by scheduling an INR monitoring 3 to 5 days apart during the first week. Thereafter, INR checking is recommended 1 week apart until its stabilization into the therapeutic range for three times. The subsequent INR checking can be scheduled once every 3 to 4 weeks (maximum 6 weeks if stable). A higher dose of warfarin should be considered in case of pediatric patients receiving total parenteral nutrition to counteract the effect of vitamin K supplementation. Monitoring INR should be preferentially performed from capillary blood with point-of-care coagulometers to overcome venipuncture trauma and to make the procedure easier and less time consuming both for children and their parents.[8]

It should be noted that there is not a maximum allowed dose of warfarin during the induction dose: indeed, the therapeutic dose of warfarin varies widely, in order of approximately 20-fold for different patients. The median weekly dosage is approximately 30 mg, with a mean reduction of 4 to 5 mg in females with respect to males.[9] However, few patients with a very low metabolism of the drug require 5 mg per week or less and, on the other hand, some patients who act as faster metabolizers require more than 100 mg per week. The need for very low or very high weekly doses not modify the indication for treatment and is not associated with a different quality of the treatment. Instead, the amount of warfarin needed to obtain a therapeutic INR should be taken into account in case of temporary treatment interruption. In some situation (i.e., warfarin-resistant patients) requiring a very high warfarin daily dose for an optimal INR value (i.e., 15–20 mg per day), it can be advisable to switch to acenocoumarol to improve the compliance and reduce the number of daily tablets. Indeed, acenocoumarol has about twice the power of warfarin requiring a maintenance dosage of 0.53 times the maintenance dosage of warfarin.[10]

Heparin Use

Warfarin is an indirect anticoagulant and needs at least 5 days to obtain effective anticoagulation. If immediate anticoagulation is required during the induction phase, a rapid-acting parenteral anticoagulant, such as low-molecular-weight heparin (LMWH) or unfractionated heparin, should be started. For patients with a 15 mL/min $<$ CrCl $<$ 30 mL/min, you would prefer to use an unfractionated heparin or a reduced dose of LMWH.[11] For patients with a CrCl $<$15 mL/min, you should use an unfractionated heparin. Immediate anticoagulation is definitely warranted in case of acute venous thromboembolism, in patients with atrial fibrillation and recent stroke and in patients with mechanical heart valves. Instead, when the thrombotic risk is sufficiently low, the indication to immediate anticoagulation is not mandatory.

Patient's thromboembolic risk can be stratified into three categories as shown in ►**Table 1**.

It is important to underline that, except for venous thromboembolism, the use of heparin is off-label in several countries, but it represents the only possible tool to achieve an immediate anticoagulant effect during warfarin induction phase.

FCSA suggests the following schemes according to patient's thromboembolic risk:

- *Low thromboembolic risk*: a rapid-acting parenteral anticoagulant (i.e., LMWH) at low-*intermediate dose** *can be associated* with warfarin for at least 5 days and until the INR value is within the therapeutic target range for at least 24 hours.

Table 1 Thromboembolic risk stratification (modified from Spyropoulos et al 2019[12])

Risk category	Mechanical heart valve	Atrial fibrillation	Venous thromboembolism
High (>10%/y risk of ATE or >10%/mo risk of VTE)	Any mechanical mitral valve Caged ball or tilting disc valve in mitral/aortic position Recent (<3 months) stroke or TIA	CHA_2DS_2VASc score ≥ 7 Recent (<3 months) stroke or TIA Rheumatic valvular heart disease	Deficiency of protein C, protein S, or antithrombin Antiphospholipid antibodies Multiple thrombophilia VTE associated with vena cava filter (active cancer)
Moderate (4–10%/y of ATE or 4–10%/mo risk of VTE)	Bileaflet AVR *with* major risk factors for stroke	CHA_2DS_2VASc score 5 or 6	VTE within past 3–12 months Recurrent VTE Nonsevere thrombophilia Active cancer or recent history of cancer
Low (<4%/y risk of ATE or <2%/mo risk of VTE)	Bileaflet AVR *without* major risk factors for stroke	CHA_2DS_2VASc score 1–4	VTE more than 12 months ago

Abbreviations: ATE, arterial thromboembolism; AVR, aortic valve replacement; mo, month; TIA, transient ischemic attack; VTE, venous thromboembolism; y, year.
Source: Adapted from Spyropoulos et al 2019[12].

- *Moderate thromboembolic risk*: a rapid-acting parenteral anticoagulant (i.e., LMWH) at *intermediate dose*[*] *can be associated* with warfarin for at least 5 days and until the INR value is within the therapeutic target range for at least 24 hours.
- *High thromboembolic risk or acute thrombosis*: a rapid-acting parenteral anticoagulant (i.e., LMWH) at full therapeutic dose must be associated with warfarin for at least 5 days and until the INR value is within the therapeutic target range for at least 24 hours.

How to Manage a Subtherapeutic INR Value in Asymptomatic Patients

The occurrence of an INR value below the lower limit of the INR target range in asymptomatic patients (i.e., without any thrombotic complication) is commonly encountered in clinical practice during warfarin treatment.

FCSA suggests considering the following items to optimally manage these patients:

- The absolute and relative (to the lower limit of the range) values of subtherapeutic INR.
- The previous value of INR.
- The time lapse between the subtherapeutic INR and the previous INR value.
- The disease-associated thromboembolic risk (see ►**Table 1**) and possible additional individual patient's thrombotic risk factors.
- The presence of interfering factors (e.g., poor compliance to therapy, interfering drugs, lifestyle change, dietary and drinking habits) that might have contributed to subtherapeutic INR.

All potential causes of subtherapeutic INR should be checked and corrected. In particular, drug adherence should be carefully assessed.

FCSA suggest to:

- Discuss with the patient again the correct timing for warfarin assumption.
- Verify if the patient has reached an adequate comprehension of the prescribed dosage.
- Assess if the patient checks the written daily therapeutic program before assumption.
- Ask who is responsible for the therapy and, if necessary, train the caregiver in warfarin management.

FCSA's practical suggestions according to the different INR therapeutic targets are summarized in ►**Tables 2** and **3**.

How to Manage a Supratherapeutic INR Value in Asymptomatic Patients

The occurrence of a high value of INR above the upper limit of the INR target range (without any bleeding complication) is commonly encountered in clinical practice during warfarin treatment.

FCSA suggests considering the following items to optimally manage these patients:

- Absolute and relative (to the upper limit of the range) values of supratherapeutic INR.
- The individual patient's bleeding risk: a multiparametric assessment including age, comorbidities, history of previous bleedings, and other concomitant antithrombotic drugs is mandatory.
- The disease-associated thromboembolic risk (see ►**Table 1**) and possible additional individual patient's thrombotic risk factors.

The following three management strategies may restore INR into the therapeutic range:

[*] LMWH at low dose means a dose of prophylaxis; LMWH at intermediate dose means 50% of the LMWH therapeutic dose.

Table 2 Practical suggestions for managing a subtherapeutic INR value in the case of an INR target range of 2.0-3.0

INR target range: 2–3				
Correct all potential causes of subtherapeutic INR value				
INR value	**Loading dose on day 1**	**Increase in warfarin weekly usual dose**	**Next INR check**	**LMWH**
1.8–1.9	25% increase of usual daily dose[a]	NO	2 weeks	NO
1.5–1.7	50% increase of usual daily dose[a]	5–10% increase[a]	1 week	[b]
<1.5	Twice the usual dose[a]	5–10% increase[a]	5–7 days	[c, d]

Abbreviations: INR, international normalized ratio; LMWH, low-molecular-weight heparin.
[a]If the patient is taking ≤6.25 mg weekly dose, consider a simple redistribution of the weekly dose, instead of a dose increase.
[b]Consider LMWH intermediate (i.e., 50% of therapeutic dose) dose in patients with high thrombotic risk. In patients with severe renal impairment (15 mL/min < CrCl < 30 mL/min), the LMWH dose must be reduced: for enoxaparin the prophylactic dose corresponds to 2,000 UI/once daily and the intermediate dose corresponds to 25% of the usual therapeutic dose (i.e., 0.5 mg/kg/once daily). In case of severe renal impairment with a CrCl < 15 mL/min, prophylactic unfractionated heparin should be used.
[c]Consider LMWH intermediate (i.e., 50% of therapeutic dose) dose in patients with moderate thrombotic risk. In patients with severe renal impairment (15 mL/min < CrCl < 30 mL/min), the LMWH dose must be reduced: for enoxaparin the intermediate dose corresponds to 25% of the usual therapeutic dose (i.e., 0.5 mg/kg/once daily). In case of severe renal impairment with a CrCl < 30 mL/min, prophylactic unfractionated heparin should be used.
[d]Consider LMWH full-dose dose in patients with high thrombotic risk. In patients with severe renal impairment with a 15 mL/min < CrCl < 30 mL/min, the LMWH dose must be reduced: for enoxaparin the therapeutic dose corresponds to 50% of the usual dose (i.e., 1 mg/kg/once daily). In case of severe renal impairment with a CrCl < 15 mL/min, therapeutic unfractionated heparin should be used.

Temporary interruption of warfarin: the length of the withdrawal depends on:

- The value of INR; the expected daily decline of INR value is around 1 point when the warfarin therapeutic dose is >25 mg/week.
- The usual weekly median warfarin dose; patients needing a low weekly dose of warfarin (i.e., <15 mg/week) are slow metabolizers with a slower clearance of the drug.
- The presence of comorbidities, such as acute heart failure, that slows warfarin clearance.

Administration of low-dose oral vitamin K (1–2 mg): it neutralizes the warfarin overdose in 18 to 24 hours by faster declining the INR to a therapeutic range without increasing later warfarin resistance. The response to vitamin K must be always verified by checking INR after 24 hours from its administration and before starting a new warfarin dosing schedule.

Check and correct all potential causes of supratherapeutic INR, such as:

- Error in dosage.
- Poor compliance/adherence.
- Concurrent illness, in particular gastroenteritis, acute heart failure, liver failure, thyrotoxicosis.
- Interfering drugs.
- Binge alcohol consumption.

All potential causes of supratherapeutic INR should be checked and corrected. When a clear cause is identified and removed/corrected, the patient should restart usual INR check interval as the INR is normalized. Instead, when no clear reason is identified, INR should be assessed at least weekly in the following weeks.

FCSA suggests managing the supratherapeutic INR according to the degree of over-anticoagulation as follows:

- *Supratherapeutic INR < 5:*
  - Day 1: reduce the daily warfarin dose by 50% up to its withdrawal according to bleeding risk.
  - From day 2: start a new warfarin dosing schedule lowered by 5 to 10% compared with the previous one. If the patient is taking ≤6.25 mg weekly dose, consider a simple redistribution of the weekly dose, instead of a dose decrease.
  - Schedule the next INR check no more than 1 week apart.

- *Supratherapeutic 5 < INR < 6:*
  - Day 1: withhold warfarin.
  - From day 2: start a new warfarin dosing schedule lowered by 5 to 10% compared with the previous one.
  - Schedule the next INR check 3 to 5 days apart.

- *Supratherapeutic INR > 6:*
  - Day 1: withhold warfarin and administer 1 to 2 mg oral vitamin K.
  - Day 2: check INR value and if INR is <5 start a new warfarin dosing schedule lowered by 5 to 10% compared with the previous one; for patients requiring low therapeutic warfarin dosage (<12.5 mg/week) withholding warfarin also on day 2 should be considered.
  - Schedule the next INR check no more than 1 week apart.

How to Manage the Association of Warfarin with Interfering Drugs

Many patients on warfarin are on treatment with other drugs. Unjustifiably, many physicians are still afraid of potential drug–drug interference and in some cases, they even withhold warfarin. However, an adequate management allows maintaining warfarin treatment with good/optimal quality even when interfering drugs are concomitantly

Table 3 Practical suggestions for managing a subtherapeutic INR value in the case of an INR target range of 2.5-3.5

INR target range: 2.5–3.5				
Correct all potential causes of subtherapeutic INR value				
INR value	**Loading dose on day 1**	**Increase in warfarin weekly usual dose**	**Next INR check**	**LMWH**
2.3–2.4	25% increase of usual daily dose[a]	NO	2 weeks	NO
1.8–2.2	50% increase of usual daily dose[a]	5–10% increase[a]	1 week	NO
1.5–1.7	50% increase of usual daily dose[a]	5–10% increase[a]	1 week	Intermediate dose[b]
<1.5	Twice the usual dose[a]	5–10% increase[a]	5–7 days	Therapeutic dose[c]

Abbreviations: INR, international normalized ratio; LMWH, low-molecular-weight heparin.
[a]If the patient is taking ≤6.25 mg weekly dose, consider a simple redistribution of the weekly dose, instead of a dose increase.
[b]In case of severe renal impairment with a 15 mL/min < CrCl < 30 mL/min, the LMWH dose must be reduced: for enoxaparin the intermediate dose corresponds to 25% of the usual therapeutic dose (i.e., 0.5 mg/kg/once daily). In case of severe renal impairment with a CrCl < 15 mL/min, prophylactic unfractionated heparin should be used.
[c]In case of severe renal impairment with a 15 mL/min < CrCl < 30 mL/min, the LMWH dose must be reduced: for enoxaparin, the therapeutic dose corresponds to 50% of the usual dose (i.e., 1 mg/kg/once daily). In case of severe renal impairment with a CrCl < 15 mL/min, therapeutic unfractionated heparin should be used.

administered. Indeed, for many drugs a possible interference has been reported, but a confirmed clinically relevant interference is known only for a limited number of drugs.[13,14] Due to their large use or very strong interfering effect, we discussed the following specific drugs.

Drugs Associated with Over-anticoagulation

- *Amiodarone*: this antiarrhythmic drug is often used in patients with atrial fibrillation. Its use is associated with supratherapeutic INRs, due to the metabolic effect on liver cytochromes. This effect is rapidly achieved when amiodarone is administered as an intravenous loading dose, while it is achieved in 2 to 3 weeks when patients do not receive a loading dose. Patients treated with amiodarone usually require a reduction of their stable warfarin therapeutic dose of approximately 20 to 30%. It should be outlined that the metabolic effect of amiodarone persists for approximately 8 weeks after the withdrawal; therefore, the patient will require a progressive but low increase in warfarin therapeutic dosage in this time frame after stopping amiodarone treatment.
- *Fluconazole*: with a similar metabolic mechanism, fluconazole rapidly reduces the liver metabolism of warfarin causing severe INR elevation. When fluconazole is started, INR should be checked after 2 to 3 days and warfarin dosage adapted accordingly.

Drugs Associated with Under-anticoagulation

- *Rifampicin*: nowadays, rifampicin is used mainly for tubercular infections and requires a very long period of treatment. Rifampicin is an inducer of the liver cytochromes and is associated with an enhanced warfarin metabolism, leading to under-anticoagulation. Patients treated with rifampicin usually require to double the standard therapeutic warfarin dose. Once the target INR is achieved by enhancing the therapeutic warfarin dose, the INR usually remains stable and patients maintain a good quality of TTR. When rifampicin is stopped, the warfarin therapeutic dose should be rapidly decreased, to reach the original therapeutic levels in 5 to 8 days.
- *Phenobarbital and carbamazepine*: these antiepileptic drugs are inducer of liver cytochrome activity and are associated with a quicker metabolism of warfarin, inducing a subtherapeutic INR. A higher dose of warfarin is required when associated, estimated in 50 to 100% of the basal warfarin dosage.

As indicated, for several other drugs, an interaction with warfarin has been reported. However, the entity of warfarin dosage variation induced is of less clinical relevance than that reported in the previous indicated conditions. A practical recommendation is to check for INR after 5 to 7 days when a potential interfering drug or a drug for which no information is available is started.

Conclusion

Although warfarin has been known for more than 80 years, its management still encloses many gray areas. In the absence of clear guidelines, we can find some answers from clinical experience and experts' opinions.

The indications provided by FCSA must be intended as suggestions of good clinical practice to support and train knowledgeable health care professionals in the field of anticoagulant therapy management with the ultimate aim of ensuring a high-quality care of patients.

What is known about this topic?

- Warfarin has long been the only oral anticoagulant drug.
- In the era of DOAC, warfarin remains the only recommended anticoagulant drug in several conditions with high thrombotic risk.

What does this paper add?

- FCSA gives some suggestions of good clinical practice for the management of warfarin in those clinical issues lacking of high-quality evidence.

Conflict of Interest

S.G. received honoraria for speaking at symposia from Pfizer and Daiichi-Sankyo and supports for attending meetings from Bayer, Daiichi-Sankyo, and Pfizer. P. B. received honoraria for lectures and/or participation on advisory board from Daiichi Sankyo, Pfizer, Bristol-Myers Squibb, AstraZeneca, Exeltis. D.B. received honoraria for lectures from Aspen and Werfen. C.A. received honoraria for lectures from Bayer. E.G. received honoraria for lectures from Sanofi and Italfarmaco, and for participation on advisory board from Roche, Sanofi Genzyme, and Novo Nordisk. G.M. received honoraria for lectures and for participation on advisory board: Bayer, Roche, Exeltis. G.R. declares no conflict of interest; A.S. received honoraria for lectures, manuscript writing, and/or participation on advisory board from Daiichi Sankyo, Bayer, Pfizer, Bristol-Myers Squibb, Boehringer Ingelheim, Sanofi, Werfen, Viatris, Alexion, and Roche. V.T. declared no conflict of interest. S.T. received honoraria for lectures and for participation on advisory board from Werfen, Stago, Italfarmaco, Pfizer, Bristol-Myers Squibb, and Sanofi. D.P. received honoraria for educational events from Pfizer, Daiichi-Sankyo, and Boehringer.

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