Medicinal Agency position in allowing both doses of dabigatran etexilate studied in RE-LY (150 mg twice daily and 110 mg twice daily), and also the U.S. Food and Drugs Administration policy of recommending the even lower 75 mg twice daily dose in selected conditions of poor renal function (1). Also for the factor (F)Xa-inhibitors rivaroxaban and apixaban, a lower dose has been used in the trials in selected conditions of poor renal function and is recommended in the current or forthcoming labels. In the phase III trial of the FXa inhibitor edoxaban in nonvalvular atrial fibrillation, 2 exposure strategies and 3 dosing regimens were tested to obtain a more personalized treatment approach. Such trial design leads to the need for a very large patient sample size in the pivotal phase III trial, which has not always been possible because it is forbiddingly expensive. A more feasible approach may be to test alternative dosing regimens after regulatory approval, that is, in the context of simple trials in a registry-like environment. This will allow a firmer documentation of the best regimens and a considerably more valid background than basing the choice of alternative regimens only on pharmacokinetic considerations. Still, there is no evidence that an individualized regimen with frequent monitoring and dose changes is either safer or more effective than a standard dose regimen, especially when using medications with a wider therapeutic window than vitamin K antagonists.

We very much warn against the proposal in the letter to extend the clinical use of these new treatments to patients with mechanical valves or hypercoagulable states based only on pharmacokinetic considerations, other than in the design of real efficacy trials. Patients with these diseases may well require drug dosing regimens different from those evaluated so far in clinical trials. Specific efficacy trials in these new settings are needed, and actually already have begun.

We certainly agree with a plea for prudence in the use of these new drugs, for which simplicity of use—undoubtedly much higher than for vitamin K antagonists—may create the illusion of absence of problems, which is certainly not the case.

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REFERENCE

1. De Caterina R, Husted S, Wallentin L, et al. New oral anticoagulants in atrial fibrillation and acute coronary syndromes: ESC Working Group on Thrombosis-Task Force on Anticoagulants in Heart Disease Position Paper. J Am Coll Cardiol 2012;59:1413–25.

The Use of ^{18}F-FDG-PET/CT in the Diagnostic Workup of CIED Infections: Another Perspective

We read with great interest the article by Sarrazin et al. (1) on the use of ^{18}F-fluorodeoxyglucose (FDG)–positron emission tomography (PET)/computed tomography (CT) in the diagnostic workup of suspected cardiovascular implantable electronic device (CIED) infections. This study indeed has great clinical potential. In fact, as noted in the accompanying editorial (2), clinicians will greatly benefit from a highly accurate diagnostic procedure to confirm CIED infection, evaluate its extent, and guide the decision whether to remove the device *versus* treating patients with antimicrobial treatment alone.

However, such an ambitious task will require more of a problem-solving approach than a single test assessment. Therefore, we believe that some comments may shed new light on the findings of Sarrazin et al. (1). The authors indicated 88.6% sensitivity and 85.7% specificity of ^{18}F-FDG-PET/CT, the latter increasing to 100% when a specific interpretation criterion (abnormal/lung ^{18}F-FDG uptake ratio $>$1.87) was applied. Considering that the authors performed ^{18}F-FDG-PET/CT in patients with a high pre-test probability, the false positive rate may be underestimated in this series. Therefore, such high specificity is achievable by adopting accurate patient selection and inclusion criteria. Indeed, the application of ^{18}F-FDG-PET/CT in patients with lower pre-test probability will rely on the high negative predictive value of the technique. In fact, up to 8% of false-positive findings has been reported in patients with pacing systems without signs of infection (3). For lower-risk patients, higher-specificity techniques such as ^{99m}Tc–hexamethylpropyleneamine oxime–leukocyte single-photon emission CT (SPECT)/CT, as recently reported for infective endocarditis (4), might be considered. In this regard, the general notion of the lower spatial resolution for SPECT/CT compared with PET/CT should consider improvements achievable with current-generation hybrid SPECT/spiral CT scanner (5,6). Finally, specific information about the type of microorganisms and data on concomitant antimicrobial treatment, particularly on the type of agents and their activity on biofilm formation (7), will help in the understanding of false-negative rates (4 cases in this paper) and therefore estimation of limitations of the test. For example, as also mentioned in the editorial, microorganisms such as *Enterococcus* and *Candida* have the ability to elude leukocyte recruitment (8,9), possibly affecting PET/CT results. Additionally, because this paper stated that 42% of patients with limited superficial skin infections at PET scan were treated with antimicrobial agents only, a higher rate as compared with the recommendation for CIED removal (10), the evaluation of microbiological results in this subgroup is critical. Considering the low rate of negative CIED pocket

JACC Vol. 60, No. 15, 2012
October 9, 2012:1430–7

cultures (14%) reported in the literature (11), either a bias in patient recruitment or in the selection of follow-up duration should also be taken into account. Therefore, microbiological, echocardiographic, and treatment information is essential to clarify the reason for the false-negative cases at ^{18}F-FDG-PET/CT, particularly for high pre-test likelihood. None of the diagnostic techniques available represent by themselves the "magic" tool: the application of patients' tailored strategies starting from the multidisciplinary comprehensive interpretation of clinical history and complete clinical characterization to identify the most suitable diagnostic test rather then the use of the single best test will be the strategy to increase the diagnostic accuracy, therefore impacting patients' management.

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REFERENCES

1. Sarrazin JF, Philippon F, Tessier M, et al. Usefulness of fluorine-18 positron emission tomography/computed tomography for identification of cardiovascular implantable electronic device infections. J Am Coll Cardiol 2012;59:1616–25.
2. Brinker J. Imaging for infected cardiac implantable electronic devices: a new trick for your PET. J Am Coll Cardiol 2012;59:1626–8.
3. Ploux S, Riviere A, Amraoui S, et al. Positron emission tomography in patients with suspected pacing system infections may play a critical role in difficult cases. Heart Rhythm 2011;8:1478–81.
4. Erba PA, Conti U, Lazzeri E, et al. Added value of ^{99m}Tc-HMPAO-labeled leukocyte SPECT/CT imaging in the characterization and management of patients with infectious endocarditis. J Nucl Med 2012;53:1235–43.
5. Mariani G, Bruselli L, Kuwert T, et al. A review on the clinical uses of SPECT/CT. Eur J Nucl Med Mol Imaging 2010;37:1959–85.
6. Mariani G, Strauss HW. Positron emission and single-photon emission imaging: synergy rather than competition. Eur J Nucl Med Mol Imaging 2011;38:1189–90.
7. Tascini C, Bongiorni MG, Di Cori A, et al. Cardiovascular implantable electronic device endocarditis treated with daptomycin with or without transvenous removal. Heart Lung 2012 Mar 20 [E-pub ahead of print].
8. Cheung GY, Rigby K, Wang R, et al. Staphylococcus epidermidis strategies to avoid killing by human neutrophils. PLoS Pathog 2010;6:e1001133.
9. Thurlow LR, Thomas VC, Narayanan S, et al. Gelatinase contributes to the pathogenesis of endocarditis caused by Enterococcus faecalis. Infect Immun 2010;11:4936–43.
10. Baddour LM, Epstein AE, Erickson CC, et al. Update on cardiovascular implantable electronic device infections and their management: a scientific statement from the American Heart Association. Circulation 2010;121:458–77.
11. Bongiorni MG, Tascini C, Tagliaferri E, et al. Microbiology of cardiac implantable electronic device infections. Europace 2012 Mar 7 [E-pub ahead of print].

Clinical Utility of ^{18}F-FDG Positron Emission Tomography and Computed Tomography in Patients With Suspected Cardiovascular Implantable Electronic Device Infection

Sarrazin et al. (1) highlighted the usefulness of positron emission tomography (PET)/computed tomography (CT) in patients with suspected cardiovascular implantable electronic device infection (CIED). The following points should be considered before reaching a final conclusion.

1. Guidelines recommend avoiding fluorodeoxyglucose (FDG)-PET scans when blood glucose level is >200 mg% in patients with cancer because hyperglycemia compromises the diagnostic ability by decreasing FDG uptake (2,3). Did the authors make an attempt to study the impact of hyperglycemia on the sensitivity and specificity of the scan because hyperglycemia is common in patients with CIED infection?
2. In the study by Sarrazin et al. (1), how many patients received antibiotic therapy before the scan and for how long of a duration? What was the impact of prior antibiotic therapy on the sensitivity and specificity of the scan?
3. Increased FDG uptake is nonspecific and may be increased in the setting of inflammation, infection, malignancy, or clot formation, whereas it may be decreased in patients with leukopenia even in the presence of infection (4,5).
4. What is the impact of the scan results on patient management? This question remains unanswered because the decision to treat was not based on scan findings. Larger-scale prospective studies with longer follow-up periods (to rule out any latent infection) are required before supporting a conservative approach for negative scans in patients with bacteremia.

Considering high scan cost, FDG-PET/CT should only be used as an adjunct diagnostic test in selective patients with CIED in whom routine workup of fever (including transesophageal echocardiography) remains inconclusive.

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REFERENCES

1. Sarrazin JF, Philippon F, Tessier M, et al. Usefulness of fluorine-18 positron emission tomography/computed tomography for identification of cardiovascular implantable electronic device infections. J Am Coll Cardiol 2012;59:1616–25.
2. Delbeke D, Coleman RE, Guiberteau MJ, et al. Procedure guideline for tumor imaging with ^{18}F-FDG PET/CT 1.0. J Nucl Med 2006;47:885–95.