Introduction. Cardiovascular diseases are very prevalent in the elderly population and characterized by high complexity, poor prognosis and comorbidity. Atrial fibrillation is common in elderly patients both in institutionalized long-term care facilities and in community associated or not to congestive heart failure, but the management with anticoagulant oral therapy is highly variable and problematic.

Case presentation. Here we describe a case report on a patient treated with amiodarone and heparine for acute atrial fibrillation episodes. Three years before he underwent partial intestinal resection for bowel cancer. During Warfarin therapy a treatment with neomycin sulphate/bacitracin was started. After three days of Warfarin therapy an International Normalised Ratio (INR) value > 10 was found. No bleeding occurred, but the period of hospitalization was prolonged. After genotype assessment for CYP2C9 and VKORC1 he was found to be an intermediate metabolizer with the genotype of CYP2C9*1/*2, and homozygous for VKORC1*2/*2. By using the International Warfarin Pharmacogenetics Consortium algorithm, the estimated therapeutic Warfarin dose was 1.8 mg/day, less than a half of prescribed dose.

Conclusion. A preventive pharmacogenetic assessment could be very useful in defining the right dose of Warfarin to be administered especially in elderly patients institutionalized in long-term care facilities with morbidity and polypharmacy.

Key words: Elderly, Pharmacogenetics, Long-term setting, Warfarin
after 300 mg IV over 1 h administration) and heparin (4000 UI/day sc) for acute atrial fibrillation episodes. After three days of Warfarin therapy he showed International Normalised Ratio (INR) values > 10. Three years before he underwent partial intestinal resection for bowel cancer, and he had suffered from hypertension and dyslipidaemia. His medications at admission included acetylsalicylic acid (ASA), ramipril, lorazepam, spironolactone, pantoprazole and nitroglycerin. His diet was unchanged, and physical examination showed that vital signs were stable. During Warfarin therapy a treatment with neomycin sulphate/bacitracin was started for acute diarrhoea. After 3 days of Warfarin therapy, the INR raised to 10.1 (Fig. 1). The treatment with Warfarin and ASA was stopped, and vitamin K administration (2.5 mg/day oral) started. Even if no bleeding occurred, hospitalization was prolonged until the patient reached full recovery. As reported by the ESC guidelines, the maintenance, safety, and effectiveness of INR within target range can be influenced by the pharmacogenetics, particularly of the cytochrome P4502C9 gene (CYP2C9) and the vitamin K epoxide reductase complex 1 gene (VKORC1). Therefore, the patient, after informed consent, was genotyped for CYP2C9 and VKORC1 by direct sequence and found to be an intermediate metabolizer with the genotype of CYP2C9*1/*2, and homozygous for VKORC1*2/*2 (low-dose Warfarin required). By using the International Warfarin Pharmacogenetics Consortium [IWPC] algorithm, that includes both clinical and genetic information, his estimated therapeutic Warfarin dose was 1.8 mg/day, less than a half of prescribed dose. After Warfarin overdosage and the pharmacogenetic determination, the patients was treated with low dose of Warfarin, and for the subsequent 5 weeks INR values fell within the 60% of optimal stable dose.

**DISCUSSION**

Defining the right dose of Warfarin to be administered in elderly patients with comorbidity and polypharmacy is not easy for clinical and pharmacogenetics reasons. Multiple studies have clearly demonstrated an increased frequency of CYP2C9 allelic variants, such as CYP2C9*2, in patients stabilized on low dose Warfarin therapy with increased probability of extremely elevated INRs and major bleeding events as compared to the general population. At the same time, the presence of VKORC1*2 polymorphism is associated with reduced VKORC1 expression, that requires lower Warfarin doses.

Whereas stratification of thromboembolic risk is the first step in the management of patients with atrial fibrillation, several studies have shown that adherence to the guidelines is not ideal, with consequent serious implications for
prognosis. In fact, although the interactions between several drugs and Warfarin are well known, in the clinical practice many drugs with the potential for drug-drug interactions are prescribed despite the warnings. For instance, amiodarone may increase the pharmacologic effects of Warfarin by inhibiting its CYP2C9 hepatic metabolism, resulting in significant hypoprothrombinemia and bleeding, with increased anticoagulant effects becoming apparent within one to several weeks, and, in poor CYP2C9 metabolizers, a higher risk of bleeding and a faster onset of the interaction. Neomycin sulphate/bacitracin are also reported to interact with Warfarin. In fact, since the drug destroys the enteric flora that synthesizes vitamin K, it is possible to observe enhanced anticoagulant activity. In this case the interaction was also complicated by a concomitant reduction of enteric surface in consequence to the previous colectomy, with changes in the absorption of nutrients. In addition, whilst a lower target INR range (1.8-2.5) has been proposed for elderly patients, probably because it is not based on large clinical trials, physicians generally do not adapt the doses of anticoagulants for old patients.

CONCLUSION

In conclusion, a global clinical evaluation and a preventive pharmacogenetic assessment with the use of a pharmacogenetic dosing algorithm (such as the IWPC) could be very useful in defining the right dose of Warfarin to be administered and, therefore, reducing the risk of an excessive increase of INR with possible bleeding complications, especially in elderly patients with comorbidity and polypharmacy.

CONSENT

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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