

constituting 25.7% of cases of left-sided native-valve IE from 1987 to 2000 and 56.1% from 2001 to 2013 ($P < .001$). The characteristics of both types of patients during the entire 27-year period are shown in Table 1. The rate of serious complications, premature mortality, and need for surgery were similar, whereas there were significant differences in epidemiological characteristics: patients with non-HDIE had a higher prevalence of non-cardiac risk factors and predisposing comorbidities (chronic gastrointestinal diseases, malignancies, renal failure, diabetes, immunosuppression) and healthcare-related procedures (intravascular catheters, and nosocomial and nosohusial EI), but less frequently had IE caused by *Streptococcus viridans* (Table 1). The characteristics of patients with non-HDIE from 1987 to 2000 and from 2001 to 2013 are shown in Table 2, highlighting significant changes in both the clinical and epidemiological profile between the 2 periods. In the most recent period, patients with non-HDIE were much older (almost 20 years older, on average), had larger vegetations, a tendency to have IE caused less by *Staphylococcus aureus* and more by *Streptococcus viridans*, and a higher prevalence of non-cardiac risk factors for IE, and more frequently had IE associated with health care procedures. The incidence of serious complications during the active phase of IE, especially of heart failure/valve dysfunction and persistent sepsis, was also significantly higher during the most recent period. Early mortality more than doubled in the second period (35.9% vs 15.4%; $P = .043$), as did the need for early surgery (69.2% vs 34.6%; $P = .002$) (Table 2).

Our data indicate that in our setting non-HDIE has shifted during the last 25 years toward a more serious clinical and prognostic profile (higher incidence of serious complications, need for surgery, and early mortality). This change may be because non-HDIE patients in the most recent period were much older and had a higher prevalence of severe comorbidities and non-cardiac risk factors for IE (chronic gastrointestinal and kidney diseases, immunosuppression, catheters and long-term vascular access). This type of IE now represents more than half of cases of native-valve IE,⁶ which may partly explain why the clinical characteristics, morbidity and mortality of non-HDIE are increasingly similar to those of HDIE, as shown in Table 1. This change also obliges us to

change our attitude toward non-HDIE, which is no longer a more “benign” disease than HDIE. Infective endocarditis without predisposing HD should be suspected in the absence of predisposing cardiac disease to allow its early diagnosis and treatment, thus helping to reduce its increasing mortality.

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Use of the New Antiplatelet Agents in Acute Coronary Syndromes: Limitations Related to Patient Characteristics



Limitaciones al uso de los nuevos antiagregantes en los síndromes coronarios agudos relacionadas con las características de los pacientes

To the Editor,

Prasugrel and ticagrelor are the drugs of choice for acute coronary syndrome, but they have a more limited profile than clopidogrel due to the risk of bleeding.¹ The percentage of patients whose clinical characteristics could limit or contraindicate the use of the new antiplatelet agents is unknown. We analyzed this percentage in a unselected cohort of consecutive patients from several Spanish centers with different forms of acute coronary syndrome.

From October 1, 2013, we studied 25 consecutive patients diagnosed with any form of acute coronary syndrome in 17 hospitals with a cardiac catheterization laboratory, 1 in each autonomous region. The only patients excluded were those taking oral anticoagulants. We studied their baseline characteristics,

antiplatelet therapy, and the characteristics that could limit or contraindicate use of the new antiplatelet agents.

Prasugrel was considered as a nonindication, based on its product information sheet, as was not performing percutaneous coronary intervention, whereas active bleeding and a history of stroke and transient ischemic attack (TIA) were considered as contraindications. Age ≥ 75 years and weight < 60 kg were considered to be limitations. According to the product information sheet, ticagrelor is contraindicated in active pathological bleeding and previous intracranial hemorrhage. On the basis of data provided by the literature, a history of TIA or nonbleeding stroke^{2,3} was considered to be a limitation, as well as moderate or severe bronchopathy⁴ and glomerular filtration rate ≤ 30 mL/h.⁵

We studied 425 patients. The baseline characteristics, treatment strategy, and antiplatelet therapy are shown in Table 1 and the conditioning factors are shown in Table 2. A total of 210 patients (49.4%) were deemed ineligible for prasugrel, 84 (19.3%) for not having undergone percutaneous coronary intervention, 139 (32.7%) for being ≥ 75 years, 15 (3.5%) for weighing < 60 kg, and 40 (9.4%) for having a history of TIA or stroke. With ticagrelor, of 82 patients (19.3%), 42 (9.9%) could have limitations due to moderate or severe obstructive pulmonary disease, 40 (9.4%) due to stroke or TIA, and 13 (3.1%) due to glomerular

Table 1
Clinical Characteristics and Antiplatelet Agents (n = 425)

Age, mean (SD), years	67.2 (12.5)
Women	119 (29.8)
Indication	
Unstable angina	92 (21.6)
Non-Q wave AMI	150 (35.3)
STEACS	183 (43.1)
Primary PCI	133 (31.3)
Stent thrombosis	8 (1.9)
Hypertension	264 (62.1)
Diabetes mellitus	155 (36.5)
Hypercholesterolaemia	217 (51.1)
Smoking	
Nonsmokers	194 (45.6)
Active smoker	149 (35.1)
Exsmokers	82 (19.3)
Previous stroke	97 (22.8)
Previous PCI	89 (20.9)
Previous revascularisation surgery	26 (6.1)
Treatment strategy	
No revascularisation	76 (17.9)
Traditional stent	137 (32.2)
≥ 1 drug-eluting stent	206 (48.5)
Revascularisation surgery	6 (1.4)
Antiplatelet therapy at discharge	
Aspirin only	8 (1.9)
Aspirin + clopidogrel	313 (73.6)
Aspirin + prasugrel	75 (17.6)
Aspirin + ticagrelor	29 (6.8)

AMI, acute myocardial infarction; PCI, percutaneous coronary intervention; SD, standard deviation; STEACS, ST-segment elevation acute coronary syndrome. Unless otherwise indicated, values express No. (%).

filtration rate < 30 mL/h. There was wide variability between centers in the use of these drugs (from 5%-60%).

Because TRITON (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel) only included patients with percutaneous interventions and recorded bleeding complications in some subgroups, the profile of prasugrel is more limited than that of clopidogrel. In our series, one third of the patients was aged 75 years or older, almost 1 of 10 had a history of TIA or stroke, and 3.5% weighed < 60 kg. Adding an extra 20% due to the absence of percutaneous coronary intervention, these aspects excluded almost half of the patients and underscore the need for attention in prescribing, as demonstrated by the PINNACLE study,⁶ an American registry of 27 533 patients treated with prasugrel, in which 13.9% had a history of TIA or stroke. These aspects can acquire particular importance in ST-segment elevation myocardial infarction, because it may be difficult to obtain a complete medical history in emergency situations.

Ticagrelor differs from clopidogrel and is similar to adenosine. In addition to its antiplatelet effect, it inhibits adenosine reuptake by red blood cells, which increases plasma concentrations. Because a benefit was demonstrated in the PLATO study (Platelet Inhibition and Patient Outcomes) both with invasive and conventional handling, ticagrelor is indicated in all types of acute coronary syndrome in the absence of contraindications such as active pathological bleeding and prior intracranial bleeding. In our series,

Table 2
Conditioning Factors for the Use of New Antiplatelet Agents

Possible conditioning factors for prasugrel use	
No indication	
No PCI	84 (19.3)
Limitations	
Age ≥ 75 years	139 (32.7)
Previous stroke or TIA	40 (9.4)
TIA	24 (5.6)
Ischemic stroke	12 (2.8)
Bleeding stroke	4 (0.9)
Weight < 60 kg	15 (3.5)
Total of patients with conditioning factors	210 (49.4)
Possible conditioning factors for ticagrelor use	
Moderate or severe obstructive bronchopathy	42 (9.9)
Previous stroke or TIA	40 (9.4)
TIA	24 (5.6)
Ischemic stroke	12 (2.8)
Bleeding stroke	4 (0.9)
Glomerular filtration rate ≤ 30 mL/h	13 (3.1)
Total patients with conditioning factors	82 (19.3)
Possible conditioning factors for the use of both drugs	67 (15.8)

PCI, percutaneous coronary intervention; TIA, transient ischemic attack. The values express No. (%).

0.9% had a contradiction due to an event of this kind in their medical history.

Based on data in the literature, we also considered the presence of moderate or severe obstructive pulmonary disease, renal failure with glomerular filtration rate < 30 mL/h, TIA, and ischemic stroke as possible limitations. In the PLATO study, 14.5% of patients on ticagrelor and 8.7% of those on clopidogrel reported dyspnea, and 0.4% and 0.3% were classified as severe.⁴ However, most cases of dyspnea are mild and, because they do not cause structural lung changes, are reversible on treatment withdrawal. Secondly, although ticagrelor is more effective in renal failure, only 214 patients with glomerular filtration rate < 30 mL/h were included, and the bleeding frequency with ticagrelor (20%) was double that of clopidogrel (10%).⁵ Finally, it also seems reasonable to consider a possible limitation in cases of previous stroke or TIA, as only 6.2% of patients with a history of these events was included, and, although the incidence of complications was low,³ there were more intracranial bleeds with ticagrelor.² In fact, in the PEGASUS study, which studied ticagrelor vs clopidogrel in 21 000 patients with a history of infarction, the sponsor excluded patients with a prior stroke. In our study, the possible limitation due to glomerular filtration rate < 30 mL/h, prior stroke or TIA, and moderate or severe bronchial disease represented 3.1%, 9.4%, and 9.9%, respectively, representing 19.5% of patients with a potential limitation.

In conclusion, apart from the financial considerations, there are other limiting factors with new antiplatelet agents in acute coronary syndrome, which could affect almost half of the patients taking prasugrel and 1 in 5 patients treated with ticagrelor. The use of the new antiplatelet agents varies greatly among hospitals.

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Death of Cardiac Origin Following Medical Visit and Discharge: What did my Patient Die of?



Fallecimiento de origen cardíaco tras visita médica y alta: ¿de qué murió mi paciente?

To the Editor,

In 2012 and 2013, there were 2942 judicial autopsies at the Barcelona and L'Hospitalet de Llobregat Forensic Pathology Centre of the Catalan Institute of Legal Medicine (*Institut de Medicina Legal de Catalunya*). Of these, 1087 patients died of violent causes (homicides, suicides, or accidents), 1835 of natural causes, and the remaining 20 required anthropological assessment.

In services such as ours, death of cardiac origin is commonly associated with sudden death. On some occasions, the death follows a recent medical visit. Autopsy is performed by court order, either at the relatives' request, or because, in the absence of a medical death certificate, the death is criminally suspicious, requiring medico-legal investigation. Given the scarcity of work on this subject, we decided to study the prodromal clinical manifestations of patients who died of cardiac cause following a hospital or home medical visit in the 72 hours prior to death.

Our results showed that there were 25 such deaths over the study period of 2012 and 2013. The deceased were 18 men (72%) and 7 women (28%), aged 31 to 86 years (mean, 64.36 years). Of these, 13 (52%) were seen as outpatients, 11 (44%) as outpatients, and 1 (4%) was seen by the Emergency Medical Service. The reasons for consultation were taken from medical records and were as follows: abdominal pain in 12 patients, precordial pain in 8 patients (1 with associated dyspnea), and syncope, anxiety, cardiac rhythm disorders, alcohol intoxication, and respiratory infection in 1 patient each. The association of symptoms with cause of death diagnosis was as follows: in 13 deaths (48%) of cardiac ischemic origin, the reasons for attendance were precordial pain in 6 patients (of these, 1 had associated dyspnea) and abdominal pain in 7. Of 4 deaths due to a ruptured aortic aneurysm, the reason for attendance was abdominal pain in 2 patients, syncope in 1, and cardiac rhythm disorders in 1. Of 3 deaths due to hypertensive cardiopathy, the reasons for attendance were precordial pain in 2 patients and abdominal pain in 1. Of 2 deaths due to dilated

cardiomyopathy, 1 patient presented with alcohol intoxication and the other with an anxiety attack. Of 2 deaths due to congestive heart failure, both patients presented with abdominal pain. One death was due to giant cell myocarditis, and the reason for attendance was respiratory infection.

Time from medical consultation to death ranged from 2 to 72 hours, with a mean time of 22.64 hours. None of the patients were reviewed by a cardiologist.

Once the results of the additional requested tests (histology and toxicology) were analyzed and combined with the autopsy findings, we concluded that the definitive causes of death were: cardiac ischemic origin in 13 patients (48%); aortic aneurysm rupture in 4 patients (16%); hypertensive cardiopathy in 3 patients (12%); dilated cardiomyopathy in 2 patients (8%); congestive heart failure in 2 patients (8%); and giant cell myocarditis in 1 patient (4%).

Of the 25 deaths, 13 were of cardiac ischemic origin (48%), unrelated to the patient's clinical treatment, since there are no clinical symptoms, electrocardiogram changes, or angiographic findings to suggest acute ischemia as the direct causal factor of death in almost 50% of sudden deaths. Most other cases of sudden death in patients with ischemic cardiomyopathy are probably caused by sustained ventricular tachycardia due to re-entry around an old infarct scar, triggering ventricular tachycardia or ventricular fibrillation.

In conclusion, the results from this descriptive study show that, despite the high number of medical acts carried out every day, in 2012 and 2013, only 25 cases of death were attributable to a cardiac cause undiagnosed at the time of recent medical review. This statement does not imply any diagnostic error, or any evaluation of clinical practice. In these cases, the complexity and seriousness of diagnostic cardiology should be taken into account,¹ since the clinical picture of an aortic aneurysm, abdominal pain, or giant cell myocarditis hamper the initial diagnosis.

Despite concern about the negative consequences of the increasing number of professional liability claims against doctors,² and, considering Gaultier's previous affirmation that within our time death would no longer be accepted as an inevitable fate,³ there were no records that relatives intended to file a medical complaint at the time of collection of the body. We acknowledge, however, the possibility that relatives may subsequently file a