Highlights

- The DDTA score, based on antiplatelet pre-treatment, age, delay and flow improvement, predicts TIMI after manual thrombectomy.
- The probability of TIMI 3 after manual thrombectomy according to the DDTA score was similar in the design and validation cohort.
- There was a linear and continuous relationship between DDTA score and all endpoints.
- Patients with DDTA ≥4 had higher rates of TIMI 3 after MT and better clinical outcomes

ABSTRACT

Background: routine manual thrombectomy (MT) is not recommended in primary percutaneous coronary intervention (P-PCI) but it is performed in many procedures. The objective of our study was validating the DDTA score, designed for selecting patients who benefit most from MT.

Methods: observational and multicenter study of all consecutive patients undergoing P-PCI in 5 institutions. Results were compared with the design cohort and the performance of the DDTA was analyzed in all patients. Primary end-point of the analyses was TIMI 3 after MT; secondary endpoint were final TIMI 3, no-reflow incidence, in-hospital mortality and in-hospital major cardiovascular events (MACE).

Results: 340 patients were included in the validation cohort and no differences were observed as compared to the design cohort (618 patients) except for lower use of MT and higher IIb/IIIa inhibitors or drug-eluting stents. The probability of TIMI 3 after MT according to the DDTA score was similar in both cohorts. The probability of TIMI 3 after MT decreased as delay to P-PCI was higher and patients presenting with >4h delay only had a predicted TIMI 3 after MT >75% if their DDTA score was >4. There was a linear and continuous relationship between DDTA score and all endpoints. Patients with DDTA ≥4 had independently higher risk of TIMI 3 after MT and lower no-reflow or in-hospital MACE or mortality.

Conclusions: the DDTA score has a high predictive value for getting TIMI 3 after MT and patients with DDTA score ≥4 had lower no-reflow and in-hospital complications.

Key words: Thrombectomy; Primary angioplasty; STEMI

Title: Multicenter and all-comers Validation of a score to select patients for manual thrombectomy, the DDTA score.

Running title: Validation of a score for manual thrombectomy selection.

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INTRODUCTION

Current guidelines for the treatment of ST-elevation myocardial infarction (STEMI) do not endorse routine manual thrombectomy (MT), with a class III recommendation[1,2]. Nonetheless, guidelines also state that there was insufficient data to assess the potential benefit of a strategy of selective MT (Class IIb, level of evidence C)[1].

MT use has declined progressively since these recommendations were published[3-5] although clinical registries reflect that it is still used in 10 to 30% of primary percutaneous coronary interventions (P-PCI) based to operators criteria[6,7]. Under the premises of the unmet need of uniform and standardized tools for decision-making on MT, we designed a simple scale to estimate the probability of successful MT in P-PCI: the DDTA score[8]. The DDTA score is based on 4 accessible variables (Dual antiplatelet treatment before the P-PCI, Delay to P-PCI, TIMI flow improvement after wiring the lesion and Age>55) and had a high-predictive capacity in the retrospective analysis of a single-center cohort. Thereafter, we designed a study to validate the DDTA score.

METHODS

The DDTA score was designed in a retrospective analysis of a single center cohort[8]. For its validation we designed an observational, multicenter and all-comers study to validate the predictive capacity of the DDTA score. The study was investigators initiated and received no external financial support. The minimal sample size was estimated to achieve 90% statistical power, with 95% confidence level and assuming that MT would not be used in more than 35% of the patients. As a result, 330 patients were considered the minimal sample size. Primary end-point of the analyses was TIMI 3 after MT; secondary endpoint were final TIMI 3, no-reflow incidence, in-hospital mortality and in-hospital MACE (Major cardiovascular events, what included death, heart failure, stroke and un-planned revascularization). The ethics committee of the coordinator institution approved the study protocol by December 2019. Five hospitals prospectively included all patients referred for P-PCI between in the following two and a half months in a unified and specific database. The individual

punctuations in DDTA score were obtained retrospectively in the analyses of the whole database according to the original report[8] (supplementary table 1).

Angiographic findings were collected according to current recommendations[9]. Successful MT was codified when TIMI 3 was observed after the device was used. MT, antiplatelet, anticoagulation or IIb/IIIa inhibitors were used according to physicians and operator's criteria. Time delays were annotated by the attending physicians according to current recommendations[2]. We used the overall delay time-to-PCI as the time from symptoms onset until wiring crossing in the P-PCI(included time to first medical contact, system activation and transfer to the cath-lab)[2]. Radial approach was the first choice, as currently recommended[9]. TIMI flow in the culprit vessel was registered at the beginning of the procedure, after wiring the lesion, after MT (when performed) and at the end of the P-PCI. No-reflow was codified according to current recommendations when there was lack of myocardial perfusion despite recanalization of the epicardial vessel[10,11].

We recorded all medical treatments that patients had received before the arrival to the cath-lab. Dual antiplatelet treatment (DAPT) was considered when aspirin was administered as well as clopidogrel, ticagrelor or prasugrel. Risk factors, clinical antecedents, previous medical treatments, complementary tests and main diagnosis at discharge were collected from all patients by trained medical staff. Major cardiovascular complications (MACE) that occurred within the hospitalization were collected prospectively from discharge medical reports and in-hospital MACE was defined by the incidence of death, stroke or un-planned revascularization (definitions 3 or 5 of the BARC consortium excluding CABG related[12,13].

Statistical analysis

Quantitative variables are presented as mean (SD) and differences were assessed by ANOVA test. Differences between variables with non-normal distribution were analyzed by Kruskal-Wallis test. Qualitative variables are presented as percentages and differences were analyzed by t-Student and Chi-square tests. The optimal cut-off value of the DDTA score was assessed by

individual characteristics item analysis. Variables associated with the endpoints were assessed by binomial logistic regressions, adjusted by age, diabetes, previous cardiovascular disease and over-all delay to PCI. The calibration of the model was assessed by the Hosmer-Lemeshow test and its predictive capacity by the area under the curve (AUC) of the diagnostic probability. The graphical representation of the probability of TIMI 3 flow after MT was performed by the individual probability obtained in multivariate analyses. Statistical difference was accepted at $p<0.05$. Data were processed with STATA 14.2 statistic package for MAC.

RESULTS

Clinical characteristics of the patients included in the design and validation phases are presented in table 1. No significant differences were observed between both phases except that the use of MT was much lower in the validation cohort. Mean DDTA score was the same in both cohorts. In-hospital mortality or MACE was the same in both cohorts. Significant differences in procedural features between both study phases were found, being DAPT pretreatment, mainly with ticagrelor, and the use of IIb/IIIa inhibitors or drug-eluting stents higher in the validation cohort.

As shown in figure 1, the probability of TIMI 3 after MT according to the DDTA score was similar in both cohorts. The threshold of DDTA score ≥4 had the highest IRT and, therefore, was used for further analyses (supplementary figure 1). To avoid the possible effect of delay to PCI categorization we assessed the probability of TIMI 3 after MT according to the DDTA score and the delay to PCI, as a continuous value. The probability decreased as delay was higher and patients presenting with ≥4h delay to PCI only had a predicted TIMI 3 after MT >75% if their DDTA score was >4 (supplementary figure 2).

There was a linear and continuous relationship between DDTA score and all endpoints. In the multivariate analyses, adjusted by age, gender, diabetes, previous cardiovascular disease and delay to PCI, the probability of TIMI 3 after MT of final TIMI 3 was higher as DDTA was higher (figure 2); the risk of no-reflow, in-hospital MACE or mortality decreased as DDTA was higher. Un-

adjusted and adjusted risks of each end-point, according to DDTA < or ≥4 are presented in table 2. Patients with DDTA ≥4 had independently higher risk of TIMI 3 after MT as well as lower no-reflow or in-hospital MACE or mortality.

DISCUSION

This study validated a simple score to predict successful MT in a multicenter and all-comers study recruited prospectively. MT use was much lower in the validation cohort, clearly in concordance with current clinical practice, but the results provide reliable evidence to support selective MT based on a simple score. Since clinical features and time delays are similar to previous reports[4,6,7,11,14-27] we believe that our results are representative of daily clinical practice.

We designed a simple score to identify which patients would benefit mostly from a technique that is not recommended to use on routine basis but can provide relevant benefits in many situations[7,20]. Thereafter, there is an unmet need of strategies for decision making on when to perform MT because, to date, there is no evidence of any specific scenario in which thrombus aspiration would be useful in terms of prognosis[28]. Randomized clinical trials[16,17] and metanalyses[11,15] have failed to demonstrate the survival improvement previously demonstrated in shorter trials[18]; therefore, routine MT is no longer recommended by clinical guidelines[1,2]. Nonetheless, MT is still used in many procedures under physicians´ criteria[4,6,7] and we believe that our results might help decision making for the selection of patients that obtain the highest benefit from this technique. MT was used less frequently in the validation cohort, in concordance with all clinical registries[4-7], but the TIMI 3 after MT was similar in both cohorts what might reflect that it was accurately performed.

The DDTA score is based on 4 variables, 3 of them might be available before the procedure (DAPT, delay and age) and the other is obtained after wiring the lesion. In the design cohort, patients consulting with >4h since symptoms onset had the lowest rates of successful MT without affecting the final TIMI 3 flow[8], what clearly suggested that longer time delays induce more thrombus organization. The effect of Ticagrelor administration before primary PCI was

tested in the ATLANTIC trial that failed to demonstrated the primary endpoint of TIMI flow 3 before PCI[29]; nonetheless, a subsequent subanalysis highlighted that the primary endpoint was reached in patients with delay >53 minutes[22]. Using the design and validation cohort we could further analyze such relationship and the risk matrix supports that patients with longer delays have much lower probability of getting TIMI 3 after MT if they have higher DDTA score. Long delays to P-PCI are frequent, they are usually related to patients preferences on consulting and, more relevantly, are associated to poorer outcomes[30,31]. Median time between symptoms onset and PCI was 190 minutes in the TAPAS trial[18], 185 minutes in the TASTE trial[16] and 173.0 minutes in the TOTAL trial[17] that are slightly shorter than in our study. Inclusion criteria for symptom onset to randomization time were <24 h in the TASTE trial[16] and <12h in the TAPAS[18] and TOTAL trial[17]. Q-waives might have higher prognostic value than time delay[27] although it was not observed in the design cohort and, therefore, was not included in the DDTA score[8]. Regional and local health care systems have largely contributed to the improvement in STEMI reperfusion[32] and shorten time delays[31] being both currently considered quality measures in STEMI systems of care.

None of current recommendations state that MT should never be performed in P-PCI[1,2]. There are no precise criteria for the assessment of which patients or conditions have the best net clinical benefit. MT has been performed in all institutions involved in the study for >10 years without any safety concerns[32,33]. Moreover, final TIMI 3 flow in our study (89.8%) was similar to the clinical trial (93.1% in the TOTAL study[17], 86% in the TAPAS trial[18]). No reflow rates were reported only in the TOTAL study (2.4%)[17] and it is much lower than in our study (6.9%). Not surprisingly, a metanalysis concluded that MT significantly increased the rate of final TIMI 3 flow by 30% and reduced no-reflow rates by 37%[11]. We suggest that these results might be even better if patients would have been selected based on the pre-test probability, the DDTA score, or, moreover, that most patients in those study would have qualified as having a DDTA score ≥4. Moreover, the stroke rate in both phases of our study was very low, as also reported in the TOTAL trial[17]. Despite such low incidence (0.7% in the MT arm vs. 0.3%) the two-fold increase risk of stroke, that has been

confirmed in the meta-analysis[11], produced a relevant alarm on MT. Our study was not powered to assess the effect of MT on stroke buy it clearly demonstrates that patients with DDTA score ≥4 have lower in-hospital MACE (including stroke) and mortality rates and could mitigate concerns related to such a feared complication as it is stroke.

MT use has decreased progressively since 2016 despite the progressive increase in P-PCI[4-6]. This is not surprising but it could also underscore that MT is being avoided in excess. For example, the meta-analysis performed by the Thrombectomy Trialists Collaboration reported that there were no significant differences in recurrent myocardial infarction, stent thrombosis, heart failure, or target vessel revascularization in patients treated with MT but patients with high thrombus burden MT was associated with fewer cardiovascular deaths (HR: 0.80; 95% CI 0.65-0.98; p=0.03)[14]. The results of MT might be improved with IIb/IIIa inhibitors[34] probably because complete retrieval of thrombus can hardly be achieved with MT alone[35]

There are several limitations to our analysis that deserve consideration. First, this is an observational study and, thus, investigates non-randomized data. Associations between various treatments and outcomes may be confounded by other uncontrolled variables. Similarly, there may have been appropriate contraindications to adjunctive pharmacotherapy or invasive angiography that were not collected. Moreover, as a multi-center study patients were treated according to local protocols and system of care that might have some differences. Nonetheless, since clinical features and complications incidence were similar to previous reports[4-7,11,14-22,36] we believe that these limitations might have not major influence on results validity.

In conclusion, the validation of DDTA score in a prospective and multicenter study verified it predictive capacity to select patients that benefit most from MT. Moreover, DDTA score ≥4 had was independently associated to higher TIMI 3 flow after MT as well as lower incidence of no-reflow, MACE or in-hospital mortality. The DDTA score calculator is available online (https://medicalc.github.io/ddta).

Acknowledgements

This study received the support of the Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), the national Spanish National Network for Biomedical Investigation on Cardiovascular Disease.

Conflict of interest

Dr. Alberto Cordero reports and a) honoraria for lectures from AstraZeneca, Bristol-Myers Squibb and AMGEN; b) consulting fees from AstraZeneca, Ferrer and AMGEN..

Dr. José Luis Ferreiro reports a) honoraria for lectures from Eli Lilly Co, Daiichi Sankyo, Inc., AstraZeneca, Roche Diagnostics, Pfizer, Abbott, Boehringer Ingelheim, Bristol-Myers Squibb and Ferrer; b) consulting fees from AstraZeneca, Eli Lilly Co., Ferrer, Boston Scientific, Pfizer, Boehringer Ingelheim, Daiichi Sankyo,Inc., and Bristol-Myers Squibb; c) research grants from AstraZeneca.

FIGURE LEGENDS

Figure 1: Probability of obtaining TIMI 3 after manual thrombectomy according to the DDTA score in both cohorts.

Figure 2: Histograms presenting the distribution of DDTA score and predicted the adjusted risk of TIMI 3 flow after MT (A), final TMI 3 (B), no-reflow (C), in-hospital MACE (D) and in-hospital mortality (D).

Suplementary figure 1: Item characteristics curve for each single punctuation of the DDTA score.

Suplementary figure 2: Predicted TIMI 3 after manual thrombectomy according to the DDTA score and delay to primary percutaneous coronary intervention.

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Figure 1

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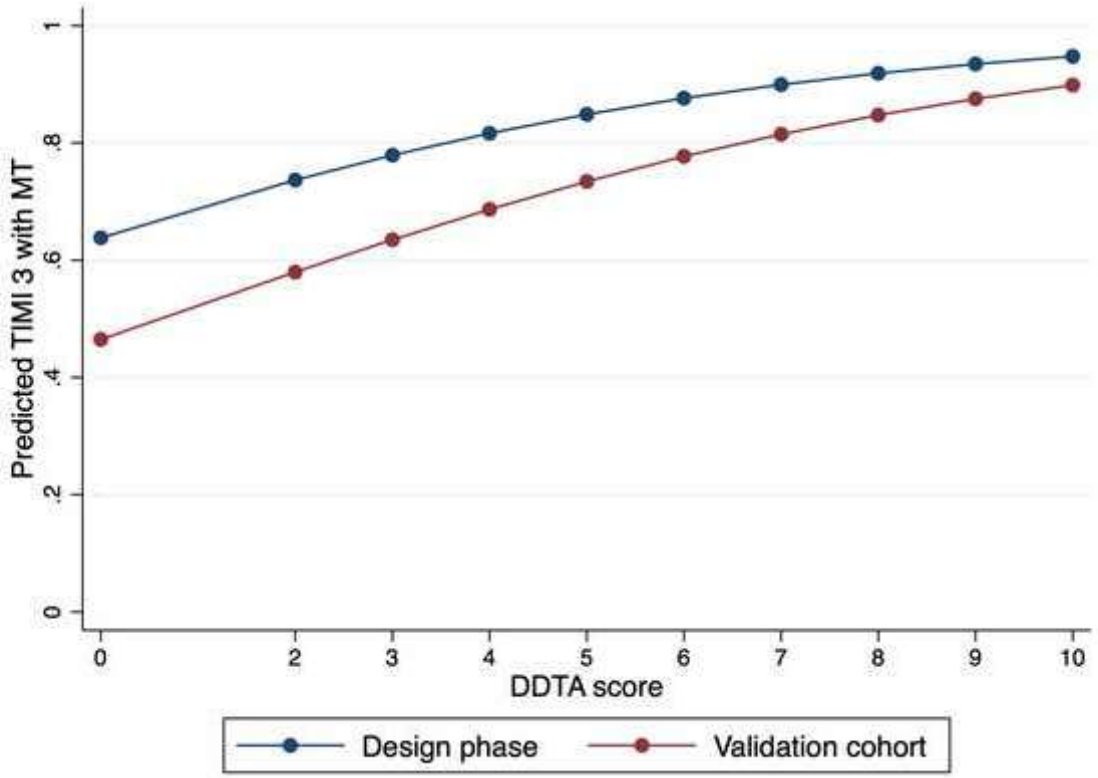

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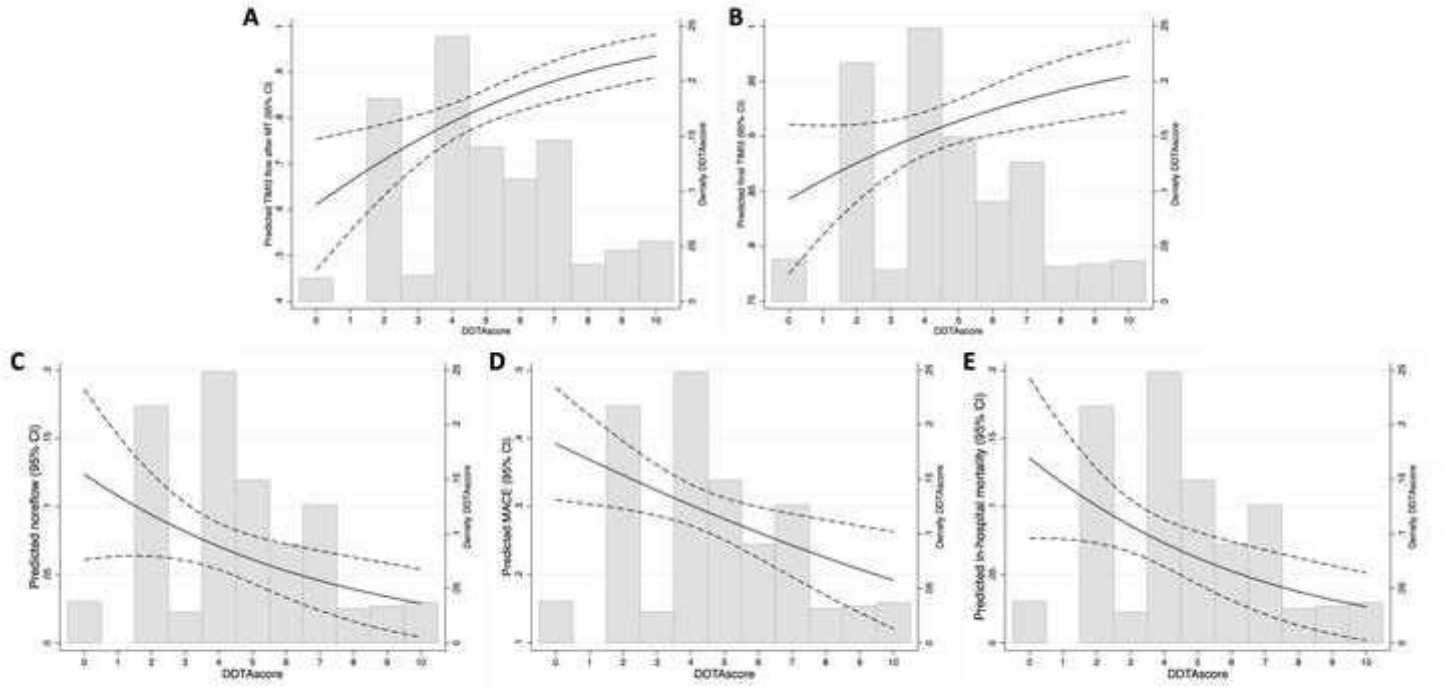

Table 1

Table 2

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Manuscript Title: **Multicenter and all-comers Validation of a score to select patients for manual thrombectomy, the DDTA score**

List of all Authors: Alberto Cordero, Belén Cid-Alvarez, Eduardo Alegría, Agustín Fernández-Cisnal, David Escribano, Jenniffer Bautista, Maria Juskova, Ramiro Trillo, Pilar Zuazola, José Luis Ferreiro.

Corresponding Author: Alberto Cordero.

This statement is to certify that all authors have seen and approved the manuscript being submitted, have contributed significantly to the work, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission to the *International Journal of Cardiology*.

We attest that the article is the Authors' original work, has not received prior publication and is not under consideration for publication elsewhere. We adhere to the statement of ethical publishing as appears in the International of Cardiology (citable as: Shewan LG, Rosano GMC, Henein MY, Coats AJS. A statement on ethical standards in publishing scientific articles in the International Journal of Cardiology family of journals. Int. J. Cardiol. 170 (2014) 253-254 DOI:10.1016/j.ijcard.2013.11).

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