International Journal of Cardiology 264 (2018) 30–38

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Duration of dual antiplatelet therapy and outcome in patients with acute coronary syndrome undergoing percutaneous revascularization: A meta-analysis of 11 randomized trials

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ARTICLE INFO

Article history:
Received 9 December 2017
Received in revised form 24 January 2018
Accepted 22 February 2018

Keywords:
Dual antiplatelet therapy
Duration
Acute coronary syndrome
Mortality
Meta-analysis

ABSTRACT

Background: Acute coronary syndromes (ACS) represent a context of higher thrombotic risk, where larger advantages have been achieved by the administration of dual antiplatelet therapy (DAPT). However, the indication of 1 year DAPT after coronary angioplasty for ACS has been supported by an outdated randomized trial (PCI-CURE). In addition, the initial fear of late thrombotic events emerged with first generation drug-eluting stents (DES), that suggested the need of a prolonged DAPT prescription, has been completely overcome by the recent technological evolution of DES, that have shown faster re-endothelization and lower rates of late thrombotic complications. By keeping in mind the balance between thrombotic and bleeding complications, and due to the paucity of dedicated randomized trials, the identification of the optimal duration of DAPT after ACS is still matter of debate, and is therefore the aim of the present meta-analysis.
Methods: Literature and main scientific session abstracts were searched. The primary efficacy endpoint was mortality, primary safety endpoint was the occurrence of major bleedings. A pre-specified analysis was conducted according to the DAPT strategy allocation (<12 vs standard 12 months duration and 6–12 months vs extended DAPT).
Results: We included 3 RCTs and subanalyses from 8 RCTs, with a total of 17,941 patients. No difference in mortality was observed between shorter vs longer DAPT (OR[95%CI] = 1.11[0.90,1.36], p = 0.33; phet = 0.76). A shorter DAPT duration significantly reduced the rate of major bleeding events (1.5%, vs 1.9%, OR [95%CI] = 0.75 [0.60, 0.94], p = 0.01; phet = 0.43). The reduction in bleeding events was more significant in trials evaluating extended DAPT duration (OR[95%CI] = 0.62[0.45, 0.85], p = 0.003; phet = 0.49). No difference in cardiovascular mortality, myocardial infarction and stent thrombosis was observed with shorter vs standard 12-moth DAPT, whereas a more extended treatment (beyond 1 year), was associated with a significant reduction in recurrent ischemic events. Similar results were observed at a sensitivity analysis conducted according to the type of stent, time to randomization or DAPT duration.
Conclusions: Based on the current meta-analysis including 17,941 ACS patients undergoing PCI, a short duration of DAPT may be safely considered, with similar rates of recurrent thrombotic complications as compared to the standard 12 months, and similar mortality. A more extended DAPT administration (beyond 1 year) provides benefits in ischemic events, but with an excess in haemorragic complications, with overall neutral effects on mortality.

1. Background

Optimal platelet inhibition represents a crucial point in the management of patients with acute coronary syndromes (ACS), and especially for those undergoing percutaneous coronary interventions (PCI) [1].

In fact, the use of more potent antithrombotic drugs and the prolongation of Dual Antiplatelet Therapy (DAPT) have been shown to reduce the rate of major adverse cardiovascular events and lower the risk of recurrent ischemic events in secondary prevention [2–4]. However, these strategies have been associated with a significant increase in major bleeding complications, with a negative impact on the expected benefits in long-term survival [5].

Besides, technological development of newer generations of drug-eluting stents (DES), providing a more rapid re-endothelialization [6] and the improvement of implantation techniques, have reduced the

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https://doi.org/10.1016/j.ijcard.2018.02.095
0167-5273/

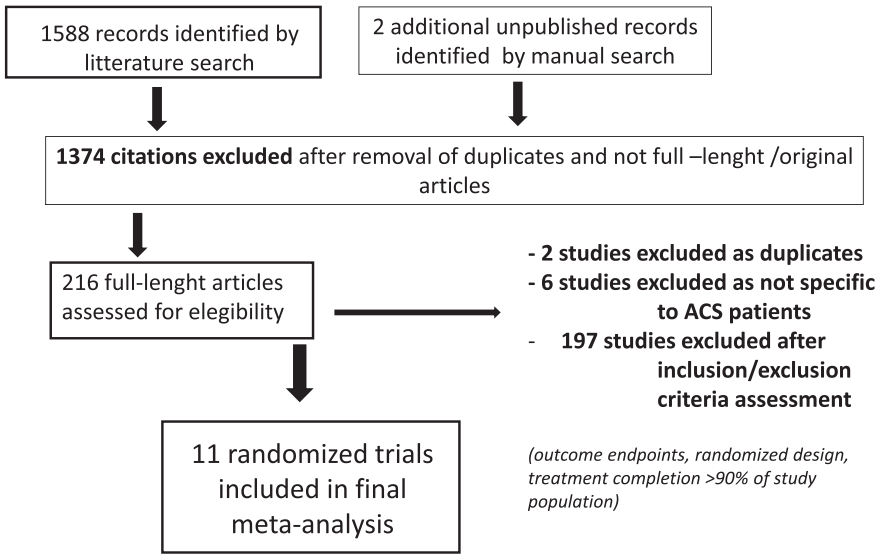

Fig. 1. Flow diagram of the systematic overview process.

risk of stent thrombosis to neglectable levels [7]. Thus, an opposite tendency to the reduction of the duration of DAPT has been pursued in the last years, especially in subsets of patients at lower thrombotic risk [8].

However, the optimal duration of DAPT has not been extensively explored in higher-risk patients, such as in the context of ACS. In fact, current recommendation of 1 year DAPT in ACS patients undergoing coronary angioplasty is still based on the PCI-CURE [9], an old trial conducted 2 decades ago. Indeed, patients at higher risk of ischemic events often represent also the subjects with the highest hemorrhagic risk [10], including those elderly, frail patients, with several comorbidities, that are a considerable proportion of patients routinely treated for an ACS in daily practice, raising the issue of the optimal balance of antiplatelet therapies in these settings. Recently two randomized trials [11,12] have documented the non-inferiority of shorter DAPT regimens as compared to the standard 12 months therapy in ACS patients undergoing PCI with newer-generations of DES.

Therefore, we aimed at performing an updated meta-analysis to evaluate the safety and effectiveness of a shorter DAPT strategy versus a standard or extended DAPT in ACS patients undergoing PCI.

2. Methods

2.1. Eligibility and search strategy

The literature was scanned by formal searches of electronic databases (MEDLINE, Cochrane and EMBASE) for clinical studies and the scientific session abstracts, searched on the TCT (www.tctmd.com), EuroPCR (www.europcr.com), ACC (www.acc.org), AHA (www.aha.org), and ESC (www.escardio.org) websites, for oral presentations and/or expert slide presentations from January 1990 to November 2017. The following key words were used: "dual antiplatelet therapy", "duration", "clopidogrel", "prasugrel", "ticagrelor", "acute coronary syndrome", "randomized".

No language restrictions were enforced. Inclusion criteria were: 1) studies with randomized allocation to different duration of DAPT treatment; 2) availability of data specific to patients with acute coronary syndrome; 3) invasive management of patients with PCI; 4) availability of complete clinical and outcome data. Exclusion criteria were: 1) follow-up data in <90% of patients, and, 2) ongoing studies or irretrievable data.

2.2. Data extraction and validity assessment

Data were independently abstracted by two investigators (MV, CC). In case of incomplete or unclear data, the authors were contacted. Disagreements were resolved by consensus. Data were managed according to the intention-to-treat principle. Data on cardiovascular mortality were collected if data on overall mortality were not available.

2.3. Outcome measures

Primary efficacy endpoint was overall mortality. Primary safety endpoint was the rate of major bleeding complications (according to protocol definition).

Secondary endpoints were: 1) cardiovascular mortality, 2) recurrent myocardial infarction, and, 3) ST (definite or probable according to Academic Research Consortium-ARC definition).

2.4. Data analysis

Statistical analysis was performed using the Review Manager 5.3 freeware package, SPSS 23.0 statistical package. Odds ratio (OR) and 95% confidence intervals (95%CI) were used as summary statistics. The pooled odds ratio was calculated by using a fixed effect model (Mantel-Haensel). The Breslow-Day test was used to examine the statistical evidence of heterogeneity across the studies ($p < 0.1$). Potential publication bias was examined by constructing a "funnel plot", in which sample size was plotted against odds ratios (for the primary endpoint). The study quality was evaluated by the same two investigators according to a score, that was expressed on ordinal scale, allocating 1 point for the presence of each of the following: 1) statement of objectives, 2) explicit inclusion and exclusion criteria, 3) description of intervention, 4) objective means of follow-up, 5) description of adverse events, 6) power analysis, 7) description of statistical methods, 8) multicenter design, 9) discussion of withdrawals, and, 10) details on medical therapy.

A pre-specified analysis was performed according to the DAPT strategy allocation (trials comparing DAPT <12 months vs the standard 12 months duration; trials comparing 6–12 months vs an extended treatment of 24–30 months).

A meta-regression analysis was carried out to evaluate the relationship between benefits in mortality (expressed as Log Odds Ratio) from