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Trials of Dual Antiplatelet Therapy After Percutaneous Coronary Intervention Lack Strategies to Ensure Appropriate Gastroprotection

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Abstract

Objectives: Gastrointestinal bleeding is a morbid complication of dual antiplatelet therapy (DAPT). We evaluated the extent to which contemporary trials of DAPT included steps to ensure appropriate use of proton pump inhibitor (PPI) gastroprotection and reported rates of PPI use.

Methods: A methodological review of randomized trials comparing varying durations of DAPT after percutaneous coronary intervention.

Results: Among 21 trials, none incorporated protocol procedures or guidance for prescribing PPIs. Five reported rates of PPI use (range 25.6-69.1%).

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Discussion: PPI gastroprotection is overlooked in major trials of DAPT. Appropriate use of PPI gastroprotection represents an important opportunity to improve patient safety.

Keywords

Dual Antiplatelet Therapy; Clinical Trial; Proton Pump Inhibitor; Gastroprotection

Introduction

The gastrointestinal (GI) tract is the most common site of clinically significant hemorrhage in patients using dual antiplatelet therapy (DAPT) (1). In such patients, proton pump inhibitors (PPIs) reduce the odds of overt or occult upper GI bleeding by approximately two-thirds (2). Accordingly, professional societies in the United States recommend PPIs for bleeding prevention in high-risk patients using DAPT, especially those with a history of upper GI bleeding (3,4), and in Europe recommend PPIs in all patients using DAPT (5). However, in clinical practice only a minority of these patients are treated with PPIs (6).

In this study, we sought to determine the extent to which contemporary clinical trials of DAPT included steps in the protocol to ensure use of PPIs to prevent upper GI bleeding.

Methods

We performed a methodological review to determine the extent to which clinical trials that evaluated the safety and efficacy of varying durations of DAPT included procedures in the study protocol or other guidance for prescribing PPIs, as well as to identify exclusion criteria related to GI bleeding risk and reported rates of PPI use. Trials of this type were selected for review because they represent a contemporary group of DAPT trials conducted during a period when high-quality evidence was available to support the use of PPI gastroprotection.

To identify relevant trials, we used a previous systematic review that investigated outcomes of varying durations of DAPT after percutaneous coronary intervention (PCI) with publication dates between June 1983 and April 2018 (7). To identify more recent trials, we repeated the identical search but limited the results to studies published between January 2018 and October 2019. The search strategy included Medline, Embase, Cochrane Library for Clinical Trials, PubMed, Web of Science, ClinicalTrials.gov, and Clinicaltrialsregister.eu. The full search strategy can be found in Supplement 1. Eligible studies were randomized controlled trials with adult participants who received DAPT following PCI with a drug-eluting stent, that compared two of three possible durations of DAPT (short-term [<6 months), standard term [12 months], and long term [>12 months]), with outcomes including death, myocardial infarction, stroke, and bleeding. Studies that evaluated ≤1 month of DAPT or included patients using oral anticoagulants were excluded.

Two authors independently reviewed all titles and abstracts to select studies for full text review (KP and ANK) and performed data abstraction (ANK and DH). A third author (JEK) adjudicated any discrepancies. For each included trial, we reviewed all available online supplementary materials, clinical trial registries, and other publications linked to the trial

NCT (clinicaltrials.gov identifier) number to identify relevant data. The review protocol was published in OSF (8).

Results

Twenty-one trials were included (Figure 1). In addition to the primary publications, study information was identified from separate trial rationale and design publications (n=7), online supplementary materials (n=13), supplementary protocols (n=4), and other publications of trial results (n=4; see Supplementary Table 2). The trials were published between 2010 and 2019 (Table 1). Sixteen trials began enrollment of patients after the 2008 publication of relevant multispecialty guidelines on PPI gastroprotection (9), and 9 trials began enrollment after the 2010 publication of the COGENT trial, which demonstrated a reduction in GI events in patients using omeprazole with clopidogrel, with no increase in cardiovascular events (10).

None of the trials included procedures in the protocol or any guidance for prescribing PPIs. One study protocol noted that PPI use was left to the discretion of the treating physician. Two study protocols specified that treating physicians could prescribe additional, non-study mandated medications but did not specifically mention PPIs. Five studies reported rates of PPI use at the time of randomization or shortly thereafter, which ranged from 25.6-69.1% (Table 2).

Trials' exclusion criteria related to bleeding are shown in Supplement 3. Nine of the trials excluded patients who had had GI bleeding or other bleeding events (without reference to an anatomic site) that occurred during some previous interval; however, none of the trials explicitly excluded patients who had such events more than one year ago.

Discussion

DAPT quadruples the risk of upper GI bleeding (11). PPI gastroprotection is recommended in DAPT patients at high risk but is underused in clinical practice (3,5,6,9). In 21 contemporary clinical trials of DAPT, a highly controlled setting in which evidence-based care is expected, none of the studies included procedures in the protocol or other guidance for prescribing PPIs to prevent upper GI bleeding, and few reported rates of PPI use. These findings highlight an important opportunity, and arguably an obligation, to improve patient safety. Systematic use of PPI gastroprotection in these trials could also lead to a better understanding of the risk-benefit profile of DAPT in the context of best practices for upper GI bleeding prevention.

It is possible that study leaders had concerns about PPIs' reducing the anti-platelet effect of thienopyridines, an interaction that has been hypothesized. However, a clinically significant interaction has not been borne out in meta-analysis (12), and professional guidance statements still recommend PPIs in high-risk DAPT patients (3). None of the trials excluded all patients at high risk for upper GI bleeding. Another possibility is unawareness of the substantial body of evidence supporting the role of PPIs for upper GI bleeding prevention. Yet, 16 of the 21 trials commenced after publication of relevant multi-society guidelines in 2008 (9), and nearly half after publication of the COGENT trial in 2010 (9,10).

As a limitation, the results of this study should not be generalized to all trials of antithrombotic drugs. In addition, it is possible that details of study procedures related to PPIs were not captured using our search strategy, but unlikely since we reviewed not only primary publications but also clinical trial registries and all available supplementary materials.

In conclusion, contemporary clinical trials of DAPT do not incorporate guideline-recommended steps to prevent upper GI bleeding, presenting an opportunity to improve patient safety, and to emphasize the importance of PPI gastroprotection to clinicians in practice. Future trials should ensure PPI gastroprotection is incorporated into study protocols.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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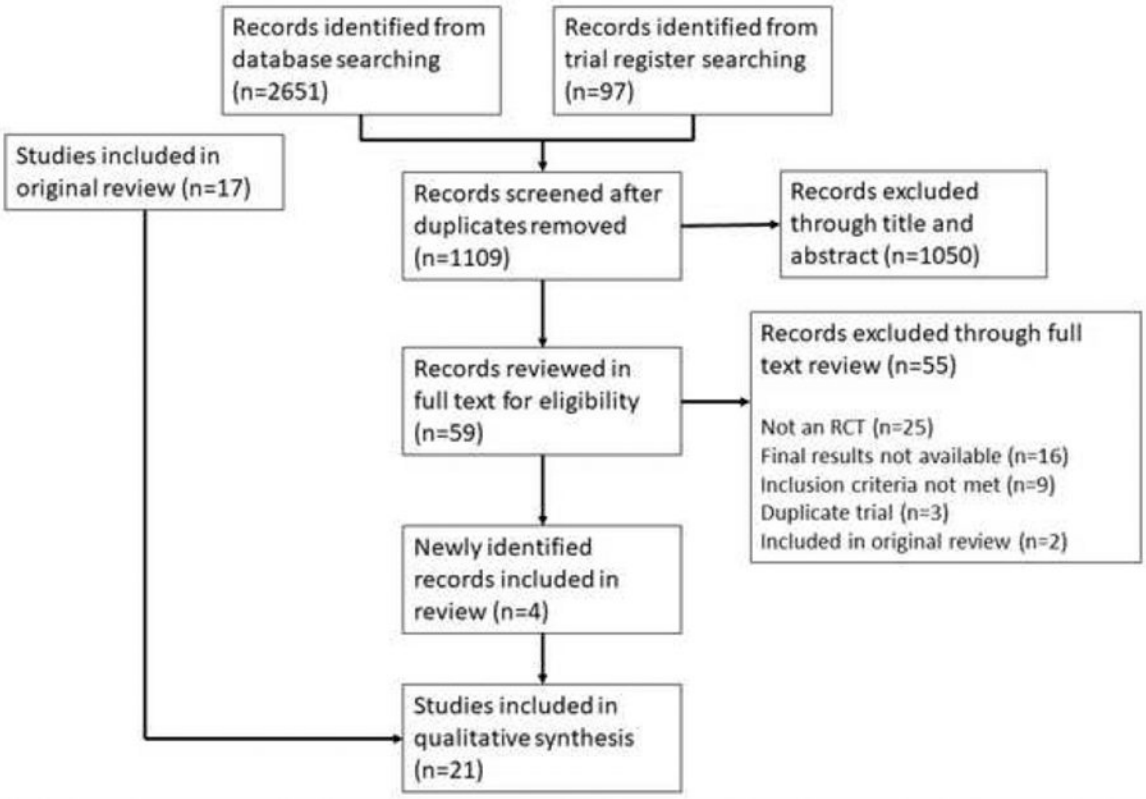

Figure 1.
PRISMA flow diagram

Table 1.

Characteristics of Included Studies

Trial Name & NCT Number	DAPT duration (months)	N	Year Published	Date of First Enrollment	Location	Study procedures regarding PPI prescribing
ARCTIC-Interruption NCT00827411	12 / 18-30	1259	2014	January 2011	38 sites in France	None
DAPT-STEMI NCT01459627	6 / 12	870	2018	December 2011	17 sites across 4 countries	None
DAPT Study NCT00977938	12 / 30	9961	2014	August 2009	452 sites in 11 countries	None
DES LATE NCT01186146	12 / 36	5045	2014	July 2007	24 sites in Korea	Stated that physicians may prescribe additional medications based on standard of care, did not specifically mention PPIs.
DETECT-OCT NCT01752894	3 / 12	779	2018	January 2013	7 sites in Korea	None
EXCELLENT NCT00698607	6 / 12	1443	2012	June 2008	19 sites in Korea	None
I-LOVE-IT 2 NCT01681381	6 / 12	1829	2016	September 2012	32 sites in China	None
ISAR-SAFE NCT00661206	6 / 12	4000	2015	October 2008	40 sites worldwide	Stated that non-study medications were prescribed at the discretion of the treating physician but did not specifically mention PPIs.
ITALIC NCT00780156, NCT01476020	6 / 24	1987	2017	November 2008	70 sites in Europe and the Middle East	None
IVUS-XPL NCT01308281	6 / 12	1400	2016	October 2010	20 sites in Korea	None
NIPPON NCT01514227	6 / 18	3307	2017	December 2011	130 sites in Japan	None
OPTIDUAL NCT00822536	12 / 48	1385	2015	January 2009	58 sites in France	None
OPTIMA-C NCT03056118	6 / 12	1367	2017	April 2011	10 sites in South Korea	None
OPTIMIZE NCT01113372	3 / 12	3119	2013	April 2010	33 sites in Brazil	None
PRODIGY NCT00611286	6 / 24	1970	2012	December 2006	3 sites in Italy	Stated that decision to start PPI left to physician's discretion.
REAL ZEST-LATE NCT00484926, NCT00590174	12 / 36	2701	2010	July 2007	22 sites in South Korea	None
RESET NCT01145079	3 / 12	2117	2012	April 2009	26 sites in Korea	None
SECURITY NCT00944333	6 / 12	1399	2014	July 2009	Multisite International Trial	None
SMART-CHOICE NCT02079194	3 / 12	2993	2019	March 2014	33 sites in Korea	None
SMART-DATE NCT01701453	6 / 12	2712	2018	September 2012	31 sites in South Korea	None
TWILIGHT NCT02270242	3 / 15	7119	2019	July 2015	187 sites in 11 countries	None

DAPT = Dual antiplatelet therapy; NCT Number = ClinicalTrials.gov identifier number; PPI = Proton pump inhibitor.

Table 2.

Prevalence of proton pump inhibitor use by assigned duration of dual antiplatelet therapy in the five studies that reported such data

Trial	Prevalence of PPI use, by assigned duration of DAPT
ARCTIC-Interruption (2014)	12 months: 29% 18-30 months: 33%
ISAR-SAFE (2015)	6 months: 26.5% 12 months: 25.6%
NIPPON (2017)	6 months: 69.1% 18 months: 67.6%
OPTIDUAL (2015)	12 months: 46.8% 48 months: 49.8%
PRODIGY (2012)	6 months: 36.9% 24 months: 38%

All studies recorded medication use prior to or at time of randomization except PRODIGY, which measured PPI use at multiple time points. The data shown are from the 30-day time point. DAPT = Dual antiplatelet therapy. PPI= Proton pump inhibitor.