Review Article on Interventional Cardiology

Oral antiplatelet therapy in the elderly undergoing percutaneous coronary intervention: an umbrella review

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Abstract: Percutaneous coronary intervention has become a mainstay in the management of coronary artery disease. While initially advanced age was considered a relative contraindication to invasive management of coronary artery disease, current cardiovascular practice stands solidly on an early invasive approach for elderly patients, typically based on radial access and drug-eluting stent implantation. Since the advent of coronary stents, oral antiplatelet therapy has proved crucial to maximize the benefits and minimize the risks of stenting, and this holds even truer in older patients rather than in younger ones. Indeed, the elderly is typically at higher risk of thrombotic events as well as bleeding complications, and thus careful decision making must be exercised to prescribe the most appropriate antiplatelet regimen. We thus conducted an umbrella review with scoping purposes on oral antiplatelet therapy in elderly patients undergoing percutaneous coronary intervention, retrieving 8 pertinent systematic reviews. We found that, while several drugs are available, ranging from aspirin to cilostazol, clopidogrel, dipyridamole, prasugrel, ticagrelor, and ticlopidine, most commonly a dual antiplatelet therapy comprising aspirin and a P2Y12 inhibitor is recommended, with subtle adjustments for pretreatment, loading, dose, duration, escalation or de-escalation, with the potential adjunct in selected patients of novel oral anticoagulants. Indeed, a flexible and individualized approach to oral antiplatelet therapy in elderly patients undergoing percutaneous coronary intervention is paramount, factoring patient features (exploiting thrombotic, bleeding and frailty scores), triage (including when appropriate non-invasive assessment of anatomic and functional significance of coronary artery disease), angiographic and other invasive imaging features, interventional technique, stent choice, rehabilitation, and secondary prevention.

Keywords: Antiplatelet therapy; aspirin; elderly; percutaneous coronary intervention

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It's not how old you are, it's how you are old

——Jules Renard

Introduction

The management of ischemic heart disease in general and coronary artery disease in particular has been recently revolutionized by concomitant breakthroughs in pathophysiologic insight, prevention, diagnosis, risk stratification, treatment and rehabilitation (1,2). Focusing specifically on management, the advent and refinement of percutaneous coronary intervention has proved hugely beneficial to patients thanks to the mirroring refinements in antithrombotic therapy (2,3). At the beginning of the percutaneous coronary intervention era potent anticoagulants were the rule before, during as well as after percutaneous coronary intervention, with ensuing high bleeding risk despite the paradox of a suboptimal prevention of acute and subacute thrombosis (4,5). Luckily enough, the central role of platelets in causing stent thrombosis was recognized eventually, and thus dual antiplatelet regimens became the key pharmacologic underpinning of percutaneous coronary intervention (6). Nowadays, percutaneous coronary intervention rests solidly on minimally invasive access (i.e., radial), simple and straightforward techniques for lesion preparation and stent implantation, followed by careful optimization of acute results (7). Devices for percutaneous coronary intervention are quite refined, with new-generation drug-eluting stents yielding very low risks of restenosis and thrombosis (8-10). Accordingly, practitioners have witnessed major developments in oral antiplatelet therapy for patients undergoing percutaneous coronary intervention, including molecule type (ranging from aspirin to cilostazol, clopidogrel, dipyridamole, prasugrel, ticagrelor and ticlopidine), front-loading strategy, maintenance dose, regimen duration, escalation, de-escalation, and combination (11). On top of this, oral anticoagulants (ranging from warfarin to apixaban, dabigatran, edoxaban and rivaroxaban) can be added to a single oral antiplatelet regimen or even to a dual antiplatelet regimen, in a framework of triple antithrombotic therapy (12). While this scenario might seem complicated at first glance, we should be reminded by ornithological principles that birds do not fly simply because they have wings, but because they go around flapping them. Accordingly, percutaneous coronary intervention successes in the individual patient strongly rest on picking for each one the most appropriate antiplatelet management strategy.

This approach indeed applies to all patients, irrespective of their age, but it is clear that elderly subjects represent a unique group, given their increased risk of adverse events as well as complications, their frequent comorbidities, and their suboptimal compliance and adherence to prescribed regimens (13,14). Most importantly, elderly patients (especially when focusing on those older than 75 or more) are typically underrepresented in clinical trials, thus requiring complex decision making based on extrapolation when planning the best antiplatelet therapy regimen before, during and after percutaneous coronary intervention (15-19).

We hereby provide a comprehensive overview of oral antiplatelet management strategy for patients undergoing percutaneous coronary intervention, with a specific focus on subjects with advanced age.

Reviewing methods

For the purpose of this review, we opted for an umbrella review design with scoping purposes (20-22). Briefly, PubMed was searched for suitable systematic reviews using the following string: (elderly OR octogenarian* OR octagenarian* OR nonagenarian OR aged OR old* OR (age AND (advanced OR higher OR older))) AND (antiplatelet* OR aspirin OR dipyridamole OR ticagrelor OR clopidogrel OR prasugrel OR ticlopidine OR cilostazol) AND ((percutaneous AND coronary AND intervention) OR ptca) AND systematic[sb]. Reviews were selected if reporting an original systematic review of clinical trials or observational studies on antiplatelet therapy for patients undergoing percutaneous coronary intervention and focusing, at least in part, on elderly subjects (i.e., those aged 65 years or more). No language restriction was enforced. Salient details on reviews, included studies and patients, interventions, and outcomes were collected. Finally, review quality was appraised using the Oxman and Guyatt Overview Quality Assessment Questionnaire (OQAQ) (21).

Main findings

Our dedicated systematic review initially retrieved 25 citations, and eventually, after excluding all non-pertinent or evidently duplicate ones at the title or abstract level, we collected 8 systematic reviews (*Table 1*) (23-30). They ranged from systematic reviews without statistical synthesis to meta-analyses and umbrella reviews, including in some instances only non-randomized controlled trials, in others only randomized trials, or both. The total number of included studies was high as 137 in the most comprehensive

Table 1 Key features of included reviews

First author	Year	PMID	Studies	Patients	Design	Focus
Bellemain-Appaix	2014	25954988	7	32,383	MA of RCTs and non-RCTs	Pretreatment with oral P2Y12 inhibitors *vs.* no pretreatment
D'Ascenzo	2014	24627967	5	49,586	MA of non-RCTs	DAPT discontinuation *vs.* continuation after PCI
Elliott	2019	31376905	16	NA	UR	Short *vs.* long-term DAPT after PCI
Khan	2018	29596078	5	6,239	MA of RCTs	PPI *vs.* no PPCI with DAPT after PCI
Lane	2013	23880057	53	187,502	MA of RCTs and non-RCTs	Combined antiplatelet and anticoagulant therapy in atrial fibrillation
Misumida	2018	30225978	10	12,696	MA of RCTs	Short *vs.* long-term DAPT after PCI
Vries	2016	26272731	38	19,667	SR of non-RCTs	Platelet function studies, genetic testing, and bleeding risk with DAPT
Zhang	2019	30629002	3	5,387	MA of RCTs	DAPT *vs.* TAT after PCI

DAPT, dual antithrombotic therapy; MA, meta-analysis; NA, not applicable; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; RCT, randomized clinical trials; TAT, triple antithrombotic therapy; UR, umbrella review.

Table 2 Internal validity of included reviews according to the Oxman and Guyatt Overview Quality Assessment Questionnaire

Item	Bellemain-Appaix [2014]	D'Ascenzo [2014]	Elliott [2019]	Khan [2018]	Lane [2013]	Misumida [2018]	Vries [2016]	Zhang [2019]
Were search methods stated? No/Partially/Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was search reasonably comprehensive? No/Can't tell/Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Were inclusion criteria reported? No/Partially/Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was bias in selection avoided? No/Can't tell/Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were validity criteria reported? No/Partially/Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was study validity assessed appropriately? No/Can't tell/Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were methods used to combine findings reported? No/Partially/Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes
Were study findings combined? No/Can't tell/Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes
Were conclusions supported by the analysis? No/Partially/Yes	Partially	Partially	Partially	Yes	Yes	Partially	Partially	Partially
How would you rate the scientific quality of this overview?	Minimal flaws	Minimal flaws	Major flaws	Major flaws	Minimal flaws	Minimal flaws	Major flaws	Minimal flawed

review, yielding as many as 313,460 patients being overviewed. In terms of validity, most reviews were of high validity, despite some noticeable drawbacks, especially in terms of search or pooling strategy (*Table 2*).

In particular, Vries *et al.* conducted a thorough systematic review on 38 observational studies including 19,667 patients receiving dual antiplatelet therapy who had undergone platelet function studies, genetic testing, or appraisal of bleeding risk (29). They found that the risk of bleeding could be predicted by identifying low on-treatment platelet reactivity by means of several different platelet function tests, by recognizing carriage of the CYP2C19*17 allele, and by using a bleeding score such as the RISK-PCI or ISTH/SSC ones. Notably, in most scores age (either

appraised as a continuous variable or as a discrete one when >70–75 years) proved a key component of bleeding scores. Bellemain-Appaix and colleagues pooled 7 randomized and non-randomized clinical trials including as many as 32,383 patients with non-ST-elevation acute coronary syndromes assigned to pretreatment with oral P2Y12 inhibitors *vs*. no pretreatment (23). They found that pretreatment with potent oral antiplatelet agents was not associated with significant changes in mortality, but caused a significant increase in the risk of bleeding.

Our group, under the leadership of Fabrizio D'Ascenzo, pooled data from 5 observational studies, including 49,586 patients with acute coronary syndromes (24). We focused on the impact of discontinuation of dual antiplatelet therapy after 12 months of uninterrupted assumption. Notably, discontinuation after 12 months appeared safe in subjects managed medically, whereas it was associated with more thrombotic events in those undergoing percutaneous coronary intervention with stent implantation. On the contrary, Misumida *et al.* pooled 10 randomized clinical trials comparing short-term (3–6 months) dual antiplatelet therapy *vs*. long-term dual antiplatelet therapy (12–24 months) in 12,696 patients with acute coronary syndromes undergoing percutaneous coronary intervention, most receiving clopidogrel and second-generation drug-eluting stents (28). They found actually that both thrombotic and bleeding events occurred with similar rates irrespective of dual antiplatelet therapy duration, despite trends in favor of long-term regimens to prevent stent thrombosis, and in favor of short-term regimens to reduce the risk of bleeding. Elliott *et al.* conducted an umbrella review quite similar in design to our present work, but different in terms of scope and focus (25). Specifically, they selected 16 systematic reviews appraising the risk-benefit balance of long-term dual antiplatelet therapy after percutaneous coronary intervention, albeit including only 8 randomized trials. They concluded that prolonging dual antiplatelet therapy beyond 1 year may reduce the risk of myocardial infarction and stent thrombosis, but may increase the risk of death and major bleeding, especially in subjects at higher risk of bleeding. Lane and colleagues published in 2013 a detailed systematic review on the combination of oral anticoagulants and oral antiplatelet agents in patients with atrial fibrillation and high-risk features (including thus coronary artery disease), totaling 53 randomized and non-randomized studies and 187,502 patients (27). They concluded that at that time there was no evidence in favor of combination therapy in such condition. However, subsequently dedicated trials have been published and should be taken into account (*Table 3*). A similar focus was found in the work

Table 3 Selected recent trials on antiplatelet therapy in patients undergoing percutaneous coronary intervention

Study	Year	PMID	Design	Setting	Focus	Main findings
AFIRE	2019	31475793	RCT	AF in stable CAD	Rivaroxaban *vs*. rivaroxaban plus OAPT	Rivaroxaban alone is safer and more effective than combination therapy
ANTARCTIC	2016	27581531	RCT	ACS in patients ≥75 years	Prasugrel 5 mg *vs*. dose/drug adjustment based on PFT on top of aspirin	Default DAPT with prasugrel 5 mg appeared similarly safe and effective to dose/drug adjustment (yielding uptake of prasugrel 10 mg in 4% and clopidogrel in 39%)
APPRAISE-2	2011	21780946	RCT	ACS	Apixaban *vs*. placebo on top of DAPT	Apixaban lead to an increase in bleedings without any significant reduction in thrombotic events
AUGUSTUS	2019	30883055	RCT	AF in ACS or PCI	Apixban *vs*. warfarin *vs*. aspirin *vs*. placebo on top of a P2Y12 inhibitor	Combination of apixaban and a P2Y12 inhibitor is safer and as effective than antithrombotic regimens including warfarin or aspirin
Claessens *et al.*	2019	31479209	RCT	Primary PCI	CYP2C19 genotype-guided selection of P2Y12 inhibitor *vs*. ticagrelor or prasugrel	CYP2C19 genotype-guided selection of P2Y12 inhibitor is as effective but safer than a default DAPT strategy including ticagrelor or prasugrel
COMPASS	2018	29132879	RCT	Stable CAD	Rivaroxaban plus aspirin *vs*. rivaroxaban alone *vs*. aspirin alone	Combined therapy with rivaroxaban and aspirin reduced death and thrombotic events albeit at an increased risk of bleeding in comparison to other strategies

Table 3 (*continued*)

Table 3 (*continued*)

Study	Year	PMID	Design	Setting	Focus	Main findings
DAPT-STEMI	2018	30279197	RCT	Primary PCI	Discontinuation of P2Y12 inhibitor after 6 months *vs*. continuation for additional 6 months	Discontinuation of P2Y12 inhibitor after 6 uneventful months following primary PCI was non-inferior to a 12-month DAPT regimen
ENTRUST-AF PCI	2019	31492505	RCT	AF in PCI	Edoxaban *vs*. warfarin on top of DAPT	Edoxaban proved non-inferior for safety and efficacy endpoint to warfarin
Gargiulo *et al.*	2016	27811064	PMA	PCI	Short-term *vs*. long-term DAPT	Short-term DAPT was safer and as effective as long-term DAPT, with the exception of a higher rate of stent thrombosis in diabetics
GEMINI-ACS	2017	28325638	RCT	ACS	Rivaroxaban *vs*. aspirin on top of P2Y12 inhibitor	Rivaroxaban was as safe as aspirin
Gibson *et al.*	2016	27959713	RCT	AF in PCI	Low-dose rivaroxaban plus P2Y12 inhibitor *vs*. very low-dose rivaroxaban plus DAPT *vs*. warfarin plus DAPT	Low-dose rivaroxaban plus P2Y12 inhibitor and very low-dose rivaroxaban plus DAPT were safer than warfarin plus DAPT
GLOBAL LEADERS	2018	30166073	RCT	PCI	DAPT for 1 month followed by ticagrelor alone for 23 months *vs*. DAPT for 12 months followed by aspirin for 12 months	DAPT for 1 month followed by ticagrelor alone for 23 months was not superior to a standard DAPT regimen for 12 months followed by aspirin monotherapy
ISAR-REACT 5	2019	31475799	RCT	ACS	Prasugrel *vs*. ticagrelor on top of aspirin	Prasugrel proved as safe but more effective than ticagrelor
PRECISE-DAPT	2017	28290994	CPS	PCI	Predictive accuracy of score encompassing age, CC, Hb, WBC, and prior bleeding	The PRECISE-DAPT score had discrimination of 0.73 in the derivation set and 0.66-0.70 in validation sets, with higher score predicting greater benefits from long-term DAPT
RE-DUAL PCI	2017	28844193	RCT	AF in PCI	Warfarin plus DAPT *vs*. dabigatran plus P2Y12 inhibitor	Dabigatran plus P2Y12 inhibitor was safer and as effective as warfarin plus DAPT
SMART-CHOICE	2019	31237645	RCT	PCI	Short-term *vs*. standard DAPT	Short-term DAPT proved non-inferior to standard DAPT
SMART-DATE	2018	29544699	RCT	ACS	Short-term *vs*. standard DAPT	Short-term DAPT proved associated with more myocardial infarctions than standard DAPT
STOPDAPT-2	2019	31237644	RCT	PCI	1-month DAPT followed by clopidogrel alone *vs*. 12-month DAPT	1-month DAPT followed by clopidogrel alone was safer and as effective than 12-month DAPT
THEMIS-PCI	2019	31484629	RCT	Stable CAD and DM	Ticagrelor *vs*. placebo in stable diabetics with prior PCI at low bleeding risk	Ticagrelor reduced thrombotic events but increased bleedings in comparison to placebo
TROPICAL-ACS	2017	28855078	RCT	ACS	12-month DAPT with prasugrel *vs*. de-escalation 14 days after discharge according to PFT	De-escalation according to PFT was as safe and as effective as standard DAPT
Yin *et al.*	2019	31253632	NMA	PCI	Short- *vs*. standard *vs*. long-term DAPT	Short-term DAPT was safer than both standard or long-term DAPT, especially when using new-generation stents

ACS, acute coronary syndrome; AF, atrial fibrillation; CAD, coronary artery disease; CC, creatinine clearance; CPS, clinical prediction score; DAPT, dual antiplatelet therapy; DM, diabetes mellitus; Hb, hemoglobin; NMA, network meta-analysis; OAPT, oral antiplatelet therapy; PCI, percutaneous coronary intervention; PFT, platelet function testing; PMA, pairwise meta-analysis; RCT, randomized clinical trial; WBC, white blood cell count.

Table 4 Key features of oral antiplatelet agents which can be used after percutaneous coronary intervention in elderly patients

Drug	Features	Pros	Cons
Aspirin	Irreversible cyclooxygenase inhibitor	Predictable risk-benefit balance, suitable for loading, inexpensive	Suboptimal potency and variability in response may increase risk of adverse thrombotic events, adverse gastrointestinal effects may increase risk of bleeding
Cilostazol*	Reversible phosphodiesterase type 3 inhibitor	May exert beneficial effect on claudication, inexpensive	Unpredictable effects in combination with new-generation antiplatelet agents
Clopidogrel	Irreversible P2Y12 inhibitor with long half-life and substantial between-subject variability in response	Predictable risk-benefit balance, suitable for loading, relatively inexpensive	Subpotimal potency and variability in response may increase risk of adverse thrombotic events
Dipyridamole*	Reversible phosphodiesterase type 3 and 5 inhibitor	Inexpensive	Unpredictable effects in combination with new-generation antiplatelet agents
Prasugrel	Irreversible P2Y12 inhibitor with long half-life and limited between-subject variability in response	Potent, suitable for loading, expensive	May be too potent in the elderly at high risk of bleeding, expensive
Ticagrelor	Reversible P2Y12 inhibitor with relatively short half-life and limited between-subject variability in response	Potent, suitable for loading, antidote available, expensive	May be too potent in the elderly at high risk of bleeding, expensive
Ticlopidine*	Irreversible P2Y12 inhibitor with long half-life and substantial between-subject variability in response	Inexpensive	Risk of hematologic complications, long half-life, moderate efficacy, subpotimal potency and variability in response may increase risk of adverse events

*, rarely used for antiplatelet purposes currently.

by Zhang and colleagues, but their restrictive selection criteria led to the inclusion of only 3 randomized trials and 5,387 patients receiving either dual antithrombotic therapy (i.e., a regimen including an oral anticoagulant and an antiplatelet agent, typically omitting aspirin) or triple antithrombotic therapy (i.e., a regimen including an oral anticoagulant and two antiplatelet agents) (30). They found that overall dual antithrombotic therapy was associated with similar rates of thrombotic events but lower rates of bleedings in comparison to triple therapy. However, when analyzing in details elderly patients, a potential increase in atherothrombotic events partially offset the reduction in bleedings associated with dual antithrombotic therapy. Finally, Khan *et al.* conducted a meta-analysis on 5 randomized clinical trials including 6,239 patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction, who had been randomized to dual antiplatelet therapy plus proton pump inhibitors *vs.* dual antiplatelet therapy alone (26). While proton pump inhibitors did not impact adversely on thrombotic events, their use was associated with significant reductions in the risk of gastrointestinal bleeding, gastrointestinal ulcers, and gastrointestinal erosions. In addition, an intriguing trend toward fewer episodes of post-revascularization unstable angina was found favoring the gastroprotection group.

Implications for patient care

The evidence so far accrued, ranging from the systematic reviews described above to the many recent trials completed on antithrombotic therapy in patients undergoing percutaneous coronary intervention, poses several major challenges to practitioners taking care of elderly subjects in whom this procedure is envisioned, as well as in those who have completed it successfully, more or less recently (13,31). Indeed, uncertainties on prediction, pretreatment, loading, genetic testing, individual agent, combination, functional testing, duration, escalation/de-escalation, and adherence persist (32-35). These challenges skyrocket when we envision the concomitant presence of comorbidities or other conditions, such as atrial fibrillation, and the unique features of the available antiplatelet agents (*Table 4*).

A pragmatic approach rests in our opinion, and

according to several experts, on refined framing of patient features, and comprehensive decision making encompassing diagnosis, risk-stratification, prognostication, warranty period definition, and invasive assessment (36-38). Once the decision to proceed with percutaneous coronary intervention is made, the choice of antiplatelet therapy should occur together with the technical planning of the revascularization procedure. Furthermore, the initial treatment plan should be periodically reviewed, allowing for escalation, de-escalation, interruption, or prolongation of the chosen antiplatelet regimen (39).

Briefly, subjects at low risk of bleeding and low risk of thrombotic events could be managed with a relatively short (e.g., 6–12 months) dual antiplatelet regimen, whereas subjects at high bleeding risk (e.g., those receiving also anticoagulant therapy) probably need even shorter regimens (e.g., 1–3 months) (40,41). Patients at high thrombotic risk and low bleeding risk can be considered eligible for refined escalation/de-escalation regimens (e.g., substituting dual antiplatelet therapy with monotherapy based on P2Y12 inhibitor), or default long-term dual antiplatelet therapy (e.g., 12 months or more), with the explicit provision that such indication can be revised if necessary or indicated by functional or genetic testing (42). Finally, dual antithrombotic therapy with a novel oral anticoagulant and a P2Y12 inhibitor is clearly the most appealing strategy in terms of risk-benefit when atrial fibrillation coexists.

Conclusions

When considering oral antiplatelet therapy for elderly patients undergoing percutaneous coronary intervention, several drugs are available, ranging from aspirin to cilostazol, clopidogrel, dipyridamole, prasugrel, ticagrelor, and ticlopidine. Yet, most commonly a dual antiplatelet therapy comprised of aspirin and a P2Y12 inhibitor is recommended, with subtle adjustments for pretreatment, loading, dose, duration, escalation or de-escalation, with the potential adjunct in selected patients of novel oral anticoagulants. Indeed, a flexible and individualized approach to oral antiplatelet therapy in elderly patients undergoing percutaneous coronary intervention is paramount, factoring in patient features (exploiting thrombotic, bleeding and frailty scores), triage, angiographic and other imaging features, interventional technique, stent choice, rehabilitation, and secondary prevention.

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Footnote

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