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Saudi Journal of Medical and Pharmaceutical Sciences
Abbreviated Key Title: Saudi J Med Pharm Sci
ISSN 2413-4929 (Print) | ISSN 2413-4910 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Original Research Article **Clinical Pharmacy**

DAPT Regimens for Elderly and Patients with Respiratory Conditions a Scoping Review

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DOI: 10.36348/sjmps.2022.v08i12.005 | **Received:** 01.11.2022 | **Accepted:** 08.12.2022 | **Published:** 10.12.2022

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Abstract

Background: Although ticagrelor is more potent than clopidogrel, it is associated with higher risk of bleeding and dyspnea. Since elderly patients are at higher risk of bleeding there is a concern of whether they should be prescribed clopidogrel instead of ticagrelor and a shorter duration of DAPT or even a monotherapy antiplatelet. Additionally, guidelines recommend being cautious when prescribing ticagrelor to COPD and asthmatic patients, yet, it is unclear whether patients with respiratory conditions are at higher risk of dyspnea from ticagrelor. This scooping review is conducted to assess the safety and efficacy of ticagrelor versus clopidogrel in elderly ≥75 years and patients with respiratory conditions. Also, to investigate the most suitable antiplatelet duration for elderly patients ≥75 years. ***Method:*** EMBASE, MEDLINE, and Cochran library were systemically searched. Studies were included if they were published in English; included adult patients diagnosed with ACS; are ≥75 years old or diagnosed with respiratory disease (asthma, COPD); treated with DAPT including clopidogrel or ticagrelor or monotherapy antiplatelet; reported quantitative data regarding bleeding or dyspnea. Studies were excluded if they were published prior to 2006. Outcome of interest were cardiovascular events, bleeding, and dyspnea. ***Results:*** 13 articles met the inclusion criteria and were included: 5 RCTs, 1 non-RCT, and 7 subgroup analyses. Two studies compared the safety and efficacy of ticagrelor versus clopidogrel in COPD patients (one of the studies included asthmatic patients), 3 studies compared safety and efficacy of ticagrelor versus clopidogrel in elderly, and 8 studies compared the duration of DAPT in elderly. ***Conclusions:*** Available data suggests that COPD and asthmatic patients are not at higher risk of dyspnea from ticagrelor and might benefit more from ticagrelor since they are at higher risk of ischemic events, yet, it is associated with higher discontinuation rate. Additionally, there was no difference between clopidogrel and ticagrelor in elderly patients in regard to cardiovascular endpoint while clopidogrel might lower the risk of bleeding. Shorter duration of DAPT might also minimize the risk of bleeding in elderly. However, data regarding DAPT in elderly and respiratory disease patients is limited, and evidence regarding the most appropriate regimen remains inconclusive.

Keywords: DAPT, P2Y12-inhibitors, bleeding, elderly, respiratory disease.

INTRODUCTION

Dual antiplatelet therapy (DAPT), an adenosine diphosphate receptor inhibitor (P2Y12-inhibitor) plus aspirin, was introduced in 2001 when the CURE trial demonstrated that adding clopidogrel to aspirin in Acute Coronary Syndrome (ACS) patients reduced major adverse cardiovascular events by 20% compared to aspirin alone [1]. However, newer generations of P2Y12 inhibitors, ticagrelor and prasugrel, achieved more rapid and significantly higher levels of platelet inhibition compared to clopidogrel [2]. Therefore, most guidelines recommend choosing ticagrelor in DAPT regimen over clopidogrel as standard treatment [3, 4].

Even though many studies showed that ticagrelor is superior to clopidogrel [3, 5, 6], the majority agreed that it is associated with higher risk of bleeding and dyspnea which eventually leads to higher discontinuation rate. Since elderly patients are at higher risk of bleeding compared to younger patients, there is a concern of whether elderly patient's ≥75 years should be prescribed clopidogrel instead of ticagrelor as a first line in DAPT in the treatment of ACS and whether they should be prescribed a shorter duration of DAPT or even a monotherapy antiplatelet. Furthermore, several studies showed that shorter DAPT regimens (<6 months) are noninferior to 12-month regimen in regard to ischemic events [2, 7, 8], and some even advocated for monotherapy antiplatelet [9].

Dyspnea is also a concern and occurred more common in patients treated with ticagrelor compared to clopidogrel. Many studies showed higher discontinuation rate in ticagrelor treated groups due to dyspnea [2, 10]. Guidelines [11, 12] recommend being cautious when prescribing ticagrelor to COPD and asthmatic patients, however, it is unclear whether patients with respiratory conditions such as asthma and COPD are at higher risk of experiencing dyspnea from ticagrelor.

The literature is lacking clear guidance in which P2Y12-inhibitor is appropriate to prescribe in DAPT for the treatment of ACS in elderly patients and patients with respiratory conditions such as asthma and COPD. Additionally, there is no clear evidence that determines whether it would be more appropriate to prescribe short period of DAPT or even monotherapy antiplatelet for elderly patients at high risk of bleeding. Therefore, the aim of this scoping review is to assess the safety and efficacy of ticagrelor versus clopidogrel and investigate which would be more appropriate for elderly ≥75 years and patients with respiratory conditions (COPD, asthma). Also, to investigate the most suitable antiplatelet duration for elderly patients ≥75 years.

METHOD

A scoping review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) [13].

Research Question

What is the most appropriate antiplatelet regimen for elderly patient's ≥75 years and patients with respiratory conditions for the treatment of ACS in regards to bleeding and dyspnea?

Search Strategy and Selection Criteria

MEDLINE, EMBASE, Cochrane library were searched by one investigator from 1 June 2020 to 10 July 2020 to identify studies reporting the safety and efficacy of ticagrelor and clopidogrel in regard to bleeding and dyspnea in a specified population, in addition to studies comparing durations of DAPT for ACS in elderly patients. Mesh terms or key search terms used were: DAPT or dual antiplatelet therapy, clopidogrel and ticagrelor or P2Y12-inhibitor, monotherapy antiplatelet and elderly, DAPT and bleeding, dyspnea or dyspnoea and respiratory conditions such as asthma and chronic obstructive pulmonary disease or COPD, DAPT duration and elderly. Additional studies were identified from reviewing bibliographies of searched articles. After removal of duplicates, a total of 1770 potential articles were identified and reviewed.

Titles and abstracts of the selected studies were reviewed to exclude any that did not research the question of interest, and full-text articles were obtained for relevant studies that met the inclusion criteria. PICOSS method was used to define the inclusion and exclusion criteria (table1). Studies were included if they were published in English; included adult patients diagnosed with ACS including unstable angina, STEMI, and NSTE-ACS; included either patients who were ≥75 years old or ≥18 years old and diagnosed with respiratory conditions such as asthma and COPD; treated with DAPT including clopidogrel or ticagrelor chosen as the P2Y12 inhibitor or monotherapy antiplatelet; reported quantitative data regarding bleeding and dyspnea. Studies were excluded if they were published prior to 2006.

Table 1

PICOSS table	
Review question	What is the most appropriate antiplatelet regimen for elderly patients ≥75 years and patients with respiratory conditions for the treatment of ACS in regard to risk of bleeding and dyspnea?
Population	Patients diagnosed with ACS including unstable angina, STEMI, and NSTE-ACS. Are either ≥75 years old OR ≥18 years old and diagnosed with respiratory conditions such as asthma and COPD
Intervention	Clopidogrel; 300-600 mg PO loading dose, then 75 mg PO once daily
Comparator	Ticagrelor; 180 mg PO loading dose, then 90 mg PO twice daily or placebo when monotherapy antiplatelet is compared to DAPT
Outcomes	Efficacy- preventing cardiovascular events including MI, stroke Safety- bleeding and dyspnea
Study design	RCTs, non-RCTs, subgroup analysis
Setting	Hospital wards, outpatient and community setting

Data Charting

Once the articles were selected, the data was extracted by one reviewer. The following data were extracted from each of the included studies: study name, design, year of publication, study population, number of participants, inclusion and exclusion criteria, and efficacy outcomes of interest (ischemic events, myocardial infarction (MI), stoke, cardiac death), safety outcomes of interest (bleeding, dyspnea), and analysis.

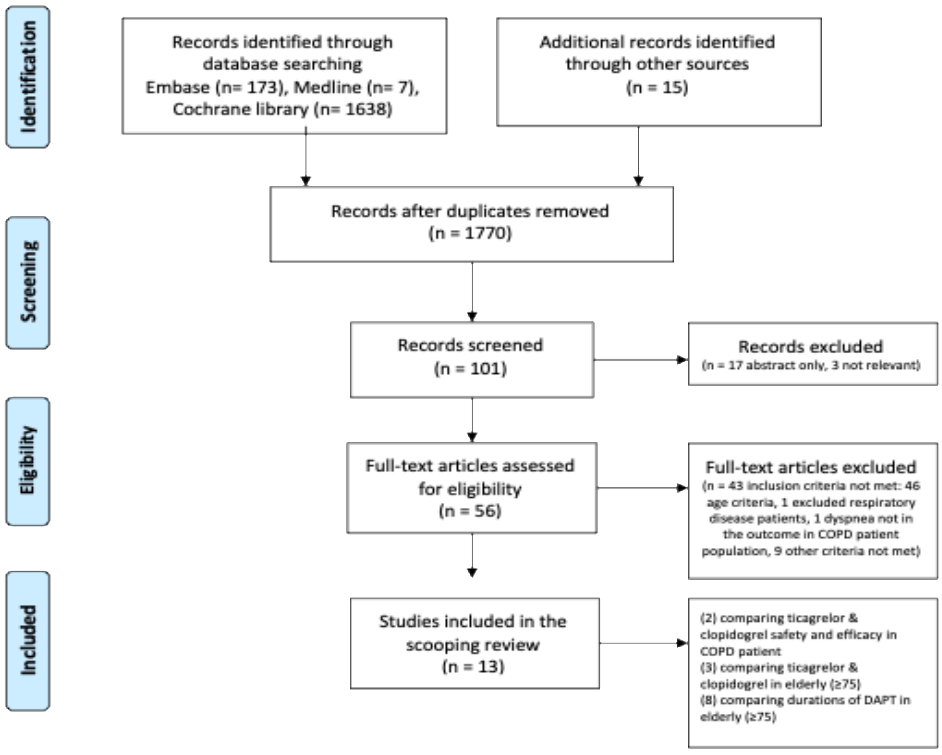
RESULTS

Research Results and Included Studies

A total of 1818 articles were identified after searching Embase, Medline, and Cochrane library and 15 articles were located from the bibliographies of searched studies. Following deletion of 63 duplicates, 101 articles were screened, and 56 articles were kept for full-text retrieval. Finally, a total of 13 articles were included in this scoping review: 5 randomized control trials (RCTs), 1 non-RCT and 7 subgroup analysis (3 post-hoc analysis, 2 pre-specified analysis, and 1 exploratory analysis). Of those 13 studies: 8 studies compared the duration of DAPT in elderly, 2 studies compared safety and efficacy of ticagrelor versus clopidogrel in COPD patients and one of them included asthmatic patients, and 3 studies compared safety and efficacy of ticagrelor versus clopidogrel in elderly (Figure 1).

Figure 1

PRISMA flow diagram describing the systematic literature search for studies comparing the efficacy and safety of ticagrelor vs. clopidogrel in elderly patients and patients with respiratory conditions/ the optimal duration of DAPT after ACS in elderly patients



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement.* PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Studies Comparing Efficacy and Safety of Ticagrelor vs. Clopidogrel in Elderly and Patients with Respiratory Conditions (Table 2)

Several RCTs that compared ticagrelor and clopidogrel efficacy and safety in ACS patients concluded that the risk-benefit profile supports using ticagrelor over clopidogrel after ACS since ticagrelor reduced the cardiovascular events (cardiac death, MI, or stroke) when compared to clopidogrel [3, 14-17]. Yet, ticagrelor increased the incidence of bleeding and dyspnea. Most of those RCTs targeted ACS population; there is a lack of studies on elderly patients who are at higher risk of bleeding and patients with respiratory conditions such as asthma and COPD who might be at higher risk of dyspnea.

Table 2: studied comparing efficacy and safety (bleeding, dyspnea) of ticagrelor vs. clopidogrel in elderly and respiratory disease patients

Trial name/author, year and study design	Sample size	Population	Primary efficacy endpoint (cardiovascular events) results	Bleeding& dyspnea results
Pontus Andell *et al.*, 2015 PLATO post-hoc analysis	1085 (5.8%) out of 18 624 patients were reported as having COPD in the PLATO trial	ACS patients with COPD	(CV death, MI, and stroke) 17.7% of COPD patients vs. 10.4% in non-COPD (P<0.001) COPD patients: 14.8% in tic vs. 20.6% in clo (HR=0.72; 95% CI: 0.54-0.97)	Dyspnea in COPD patients: 26.1% Tic vs. 16.3% Clo (HR=1.71; 95% CI: 1.28 to 2.30). No differential increase in the relative risk of dyspnea compared to non-COPD patients (HR=1.85). Major bleeding rates in COPD patients: 14.6% Tic vs. 16.6% Clo
Robert F. Storey *et al.*, 2011 PLATO post-hoc analysis	Occurrence of dyspnea was analyzed in 18421 patients	ACS	(CV death, MI, and stroke) 8.8% Tic vs. 10.4% Clo	Dyspnea: 1339 (14.5%) Tic vs.798 (8.7%) Clo. 39 (0.4%) and 24 (0.3%) was classified as severe respectively.
POPULAR-AGE, 2020 RCT	1002	NSTEMI-ACS	(all- cause death, MI, stroke) 139 (28%) Clo vs. 161 (32%) Tic; absolute risk difference –4%, 95% CI –10·0 to 1·4; p=0·03 for non-inferiority.	Major or minor bleeding: 88 (18%) in the Clo vs. 118 (24%) in Tic; HR 0·71, 95% CI 0·54 to 0·94; p=0·02 for superiority)
Steen Husten *et al.*, 2012 PLATO prespecified analysis	18622 (2878 patients ≥75 years, 15744 patients <75 years)	ACS	(CV death, MI, and stroke) ≥75 years: 17.2% Tic vs. 18.3% Clo (HR, 0.89; 95% CI, 0.74–1.08)	Major bleeding: ≥75 years: 14.2% Tic vs. 13.5% Clo <75 years:11.2% Tic group vs. 10.8 Clo (p=0.89) Dyspnea: ≥75 years: 18.8% in Tic vs. 12.2% in Clo <75 years: 14.2% in Tic vs. 7.8% in Clo (p=0.21)
Paolo Zocca *et al.*, 2018. Analysis of CHANGE-DAPT	2062 (547 (26.5%) HBR)	ACS	(CV death, MI, and stroke) HBR: 1.7% Clo vs. 5.0% Tic (HRadjusted: 3.70, 95% CI 1.18–11.67, p = 0.03 Non-HBR: 2.8% Clo vs. 3.4% Tic (HRadjusted: 1.38, 95% CI 0.74–2.57, p = 0.32)	Major bleeding: HBR: 6.6% Clo vs. 8.0% Tic (HRadjusted: 1.23, 95% CI 0.63–2.42, p = 0.54) Non-HBR: 1.1% Clo vs. 1.7% Tic (HRadjusted: 2.13, 95% CI 0.84–5.43, p = 0.11)

Tic: ticagrelor group, Clo: clopidogrel group, MI: myocardial infarction, CV= cardiovascular, HBR= high bleeding risk, CI = confidence interval. HR = hazard ratio, COPD: chronic obstructive pulmonary disease

- **Dyspnea Risk in Respiratory Disease Patients**

ACS patients with COPD are at high risk for cardiovascular events [18]. Even though ticagrelor is more potent than clopidogrel and might be more beneficial for them, some clinicians avoid ticagrelor from COPD patients due to higher dyspnea rate [19]. However, it is not clear if COPD is a precipitating factor for ticagrelor induced dyspnea. Therefore, a post-hoc analysis of the PLATO trial [19] was conducted in 2015 to study the efficacy and safety profile of ticagrelor versus clopidogrel in ACS patients with COPD. In the PLATO trial, 1085 (5.8%) were reported as having COPD out of 18624 patients. The study showed that dyspnea occurred more frequently with ticagrelor in COPD patients when compared to clopidogrel (26.1% vs. 16.3%; HR: 1.71; CI: 1.28-2.30). However, the risk of dyspnea was not higher in in COPD patients compared to non-COPD patients (HR=1.85). Overall, discontinuations rate was low, yet, COPD patients treated with ticagrelor showed higher discontinuation rate due to dyspnea compared to non-COPD patients (2.5% vs. 0.9%; interaction P-value= 0.616). The post-hoc analysis also revealed that COPD patients encountered higher rates of ischemic events and that ticagrelor decreased the risk of ischemic events for them, without increasing overall major bleeding events. The study concluded that the benefit-risk profile supports using ticagrelor in ACS patients with COPD.

Furthermore, a previous post-hoc analysis of the PLATO trial [20] was conducted in 2011 to report the frequency of dyspnea and its relation to demographic characteristics and clinical outcomes in ACS patients treated with ticagrelor or clopidogrel. Occurrence of dyspnea was analyzed in a total of 18421 patients. At enrolment, 1890 patients in the ticagrelor group had a history of dyspnea (790 is from heart failure (HF), 330 is from COPD, 125 is from asthma), and 1856 patients in the clopidogrel group had a history of dyspnea (803 is from HF, 291 is from COPD, 131 is from asthma). After randomization, dyspnea was reported in 1339 (14.5%) patients in the ticagrelor group (318 HF, 81 COPD, 13 asthma) and 798 (8.7%) patients in the clopidogrel group (246 HF, 42 COPD, 6 asthma). Only 39 (0.4%) in the ticagrelor group and 24 (0.3%) in the clopidogrel group were severe. Discontinuation due to dyspnea was higher in the ticagrelor group 79/1339 (5.9%) versus 13/798 (1.6%) (P=0.0001). Eventually, patients with a history of COPD or asthma are not at higher risk of developing ticagrelor-induced dyspnea compared with those without a history of these conditions.

- **Bleeding Risk in Elderly**

The POPULAR-AGE (21) study included 1002 patient and revealed that the risk of bleeding in elderly patients ≥70 with NSTEMI-ACS can be significantly lowered when clopidogrel is used instead of ticagrelor (18% vs. 24%; HR 0.71, 95% CI 0.54-0.94; p=0.02 for superiority) without increasing the cardiovascular events (28% in clopidogrel group vs. 32% in ticagrelor group; absolute risk difference –4%, 95% CI –10.0 to 1.4; p=0.03 for non-inferiority) . The study concluded that elderly patients might benefit from clopidogrel since they are at higher bleeding risk. Contrary, a sub study prespecified analysis of the PLATO trial [22] revealed that the risk of major bleeding complications in patients ≥75 years was similar between the ticagrelor and clopidogrel group (13.5% in clopidogrel group vs. 14.2% in ticagrelor group; HR: 1.02, 95% CI: 0.82-1.27), with similar cardiovascular events rate (17.2% in ticagrelor group vs. 18.3% in clopidogrel group; HR: 0.89; 95% CI: 0.74– 1.08). Also, the significant clinical benefit and overall safety of ticagrelor compared with clopidogrel does not depend on age.

Furthermore, an analysis of the CHANGE-DAPT [23] trial was conducted to assess if excess bleedings with ticagrelor is restricted to high bleeding risk (HBR) patients which includes patient's ≥75 years. Study results showed that the rate of major bleeding was significantly higher during ticagrelor when compared with clopidogrel (5.0% vs. 1.7%; HRadjusted: 3.70, 95% CI: 1.18–11.67, p = 0.03) with no significant difference in cardiovascular events (6.6% in clopidogrel period vs. 8.0% in ticagrelor period, HRadjusted: 1.23, 95% CI: 0.63– 2.42, p = 0.54) in HBR patients. Yet, in non-HBR patients, the rates of major bleeding and cardiovascular events were similar between ticagrelor and clopidogrel (major bleeding: 1.1% clopidogrel vs. 1.7% ticagrelor; HRadjusted: 2.13, 95% CI: 0.84– 5.43, p = 0.11/ ischemic endpoint: 2.8% clopidogrel vs. 3.4% ticagrelor, HRadjusted: 1.38, 95% CI: 0.74–2.57, p = 0.32). The analysis concluded that the high risk of major bleeding with ticagrelor was restricted to HBR patients.

Results of Studies Comparing Durations of DAPT and Monotherapy (Table 3)

Elderly patient's ≥ 75 years of age have been underrepresented among clinical trials that evaluate different durations of DAPT following PCI for ACS, while the number of elderly patients is expected to grow with ageing population. Many trials showed that shorter DAPT duration (3- 6-months) is non-inferior to long DAPT duration (≥ 12-months) in ACS patients without specifying elderly patients [24-34]. Therefore, there is a need to identify the most suitable antiplatelet regimen for elderly patients since they are at higher risk of bleeding as seen in clinical practice. Additionally, monotherapy antiplatelet protocols (must protocols include at least 1-month of DAPT), especially after PCI with drug eluting stent (DES), have been advocated to preserve their anti-ischemic effects without the bleeding risk [35-37].

Table 3: studies comparing durations of DAPT in elderly patients

Trial name/author, year and study design	Sample size	Study intervention	Population	Primary efficacy endpoint (CV)	Safety endpoint (bleeding only)
SENIOR, 2017 Randomized single-blind trial	1200 ≥75 years	1 month of DAPT in stable or silent cases and 6 months in unstable cases. Then patients were randomly assigned to PCI with a DES or a BMS.	stable angina silent ischemia ACS	(All-cause mortality, MI, stroke, or ischemia-driven target lesion revascularization) 12% in DES 16% in BMS (RR 0.71, 95% CI 0.52-0.94, p=0.02)	Bleeding complications: 26 [5%] in the DES group 29 [5%] in the BMS group (RR 0·90, 95% CI 0·51–1·54, p=0·68)
Mariusz Tomaniak *et al.*, 2020 Prespecified analysis of the GLOBAL-LEADERS	2565 ≥75 years	1-month DAPT, then 23-month ticagrelor monotherapy vs. 12-month DAPT followed by 12 months of aspirin	ACS and stable CAD	(2-year all-cause mortality or new Q-wave core lab-adjudicated MI) 7.2% in the ticagrelor monotherapy group 9.4% in the 12-month DAPT group (HR 0.75, 95%, CI: 0.58-0.99, p=0.041)	BARC-defined bleeding type 3/5 occurred in: 5.2% in the ticagrelor monotherapy group 4.1% in the 12-month DAPT group (HR 1.29, 95% CI: 0.89-1.86; p=0.180)
LEADER-FREE, 2015 double-blind RCT	2466 HBR (includes patients ≥75 years)	1-month DAPT with drug-coated stent or bare-metal stent	CAD with an indication for PCI.	(Cardiac death, MI, or ST) 112 (9.4%) in the drug-coated–stent group 154 (12.9%) in the bare-metal–stent group (risk difference, −3.6 percentage points; 95% CI, −6.1 to −1.0; HR, 0.71; 95% CI, 0.56 to 0.91; P<0.001 for noninferiority and P=0.005 for superiority)	BARC 3–5 85 (7.2) in the drug-coated–stent group 85 (7.3) in the bare-metal–stent group (HR 0.99 (95% CI, 0.73–1.34) p=0.96)
ZEUS, 2015 Single blind RCT	1606 HBR (includes patients >80 years) or thrombosis	ZES or BMS with a personalized 1-month DAPT	ACS and stable CAD	(1-year major CV events: death, MI, or target vessel revascularization) 140 (17.5%) in the ZES group 178 (22.1%) in the BMS group (HR: 0.76; 95% CI: 0.61- 0.95; p=0.011)	BARC classifications (5,3, or 2) 41 (5.1) in the ZES group 53 (6.6) in the BMS group
Hirotoshi Watanabe *et al.*, 2020 post-hoc analysis of STOPDAPT-2	3009 (1054 HBR, 1955 non-HBR)	1-month DAPT then clopidogrel monotherapy in HBR and non-HBR Vs. 12-month DAPT (aspirin + clopidogrel) in HBR and non-HBR	ACS patient receiving PCI	(1-year composite of CV death, MI, ST, or stroke) no significant interactions between HBR/non-HBR groups on the primary endpoint: HBR: 3.48% in the 1-month DAPT group vs. 5.98% in the 12-month DAPT group (HR 0.57, 95% CI 0.32–1.03) non-HBR: 1.81% in the 1-month DAPT group vs. 2.36% in the 12-month DAPT group (HR 0.78, 95% CI 0.42–1.45; *P* for interaction = 0.48)	TIMI major/minor bleeding HBR: 0.41% in the 1-month DAPT group vs. 2.71% in the 12-month DAPT group (difference − 2.30%, 95% CI − 3.77 to − 0.83%, HR 0.15, 95% CI 0.03–0.65, *P* = 0.01) Non-HBR: 0.40% in the 1-month DAPT group and in 0.85% in the 12-month DAPT group (absolute difference − 0.45%, 95% CI − 1.16 to 0.26%, HR 0.48, 95% CI 0.14–1.58, *P* = 0.22)

Trial name/author, year and study design	Sample size	Study intervention	Population	Primary efficacy endpoint (CV)	Safety endpoint (bleeding only)
Raffaele Piccolo *et al.*, 2017 Analysis of the PRODIGY trial	1970 (587 ≥75 years, 1383 <75 years)	6-month DAPT vs. 24-month DAPT in patient ≥75 years and <75 years	ACS patient receiving PCI	(Death, MI, CVA) <75 years: 7.1% in the 24-month DAPT group, 4.9% in the 6-month DAPT group (HR: 1.48; 95% CI 0.95-2.30; P=0.08) ≥75 years: 17.7% in the 24-month DAPT group, 21.4% in the 6-month DAPT group (HR: 0.80; 95% CI 0.55-1.16; P=0.24)	(BARC type 2, 3 or 5 bleeding) <75 years: 6% in the 24-month DAPT group, 2.4% in the 6-month DAPT group (HR: 2.54; 95% CI 1.43-4.53; P=0.002) ≥75 years: 12% in the 24-month DAPT group, 18% in the 6-month DAPT group (HR: 1.90; 95% CI 1.06-3.38; P=0.03)
MASTER- DAPT, ongoing RCT,	Estimated 4300 HBR (includes patients ≥75 years)	1-month DAPT then 11-month single antiplatelet Vs. 12-month DAPT	coronary heart disease with a drug covered stent	(All-cause death, MI, stroke) NA	(BARC classification types 3 or 5) NA
EVOLVE short DAPT, ongoing prospective single-arm study	2009 HBR (includes patients ≥75 years)	3-months DAPT then aspirin if free from stroke, MI, revascularization, ST	ACS	(Death from any cause, MI, ST) NA	(BARC classification types 2,3 and 5) NA

DES = drug-eluting stent, ZES = zotarolimus-eluting stent, MI = myocardial infarction, DAPT = dual antiplatelet therapy, CI = confidence interval. HR = hazard ratio, HBR= high bleeding risk, NA= not available, CV= cardiovascular, CVA= cerebrovascular accident

Shorter DAPT duration, as short as 1-month, in elderly patients after DES was shown to be effective and safe in the LEADERS-FREE [35] and ZEUS [36] trials where both included HBR patients (included patient's ≥75 years and >80 years, respectively) that were given only 1-month of DAPT, in addition to the new SENIOR trial [37] which included patients≥75 years of age and were prescribed DAPT for 1-month in patients with stable presentation or 6-months in ACS patients.

The above clinical trials compared different stents with short DAPT durations. However, a post-hoc analysis of the STOPDAPT-2 trial [38] compared DAPT durations in HBR patients mainly to define the best DAPT duration after PCI using DES. It showed that 1-month DAPT is more beneficial than 12-month DAPT in reducing bleeding in HBR patients than in non-HBR patients (BARC 3 bleeding in HBR; 0.4% 1-month vs. 2.71% 12-month, HR: 0.15, 95% CI: 0.03–0.65, p=0.01/ in non-HBR; 0.50% 1-month vs. 0.96% 12-month, HR: 0.53, 95% CI: 0.18–1.57; p= 0.25). Similar results were seen in an analysis of the PRODIGY trial [40] but it was comparing 6-months DAPT versus 24-months DAPT. The study found that prolonging DAPT beyond 6- months in elderly patients increased the risk of bleeding, without significantly preventing ischemic events. Additionally, a prespecified subgroup analysis of the GLOBAL-LEADERS trial [39] trial evaluated ticagrelor monotherapy safety and efficacy in patient's ≥ 75 years. In the study, patients ≥ 75 years with ACS had no difference in the rates of the primary ischemic endpoint (7.2% in ticagrelor monotherapy group vs. 9.4% in the 12-month DAPT group, HR: 0.75, 95% CI: 0.58-0.99, p=0.041) or the key safety endpoint of BARC 3 or 5 type bleeding (5.2% in the ticagrelor monotherapy group vs 4.1% in the 12-month DAPT group, p=0.180). However, the definite/probable/possible ST was lower in the ticagrelor monotherapy group (4.7% vs. 3.8%, HR: 0.51. 95% CI: 0.31-0.85, p=0.010).

Two ongoing RCTs were included in this scooping review. The MASTER- DAPT [41] is comparing short (1-month) versus long (12-month) DAPT in HBR patients including patient's ≥ 75 years of age. And the EVOLVE short DAPT [42], a prospective single-arm study, discontinued the P2Y12-inhibitor antiplatelet and continued aspirin monotherapy after 3-months of DAPT for patients free from stroke, MI, revascularization and stent thrombosis.

DISCUSSION

This scoping review was performed to review the existing literature that identifies the most appropriate antiplatelet regimen for elderly patient's ≥75 years and patients with respiratory conditions for the treatment of ACS in regard to risk of bleeding and dyspnea. A total of 13 articles were included.

Ticagrelor Induced Dyspnea in Respiratory Disease Patients

Only two studies were found comparing ticagrelor versus clopidogrel in COPD patients and one of them included asthmatic patients, both of which are post-hoc analyses of the PLATO trial that were not prespecified in the original trial design. This points a significant need for further studies focusing on assessing the risk of dyspnea in patients with respiratory conditions, mostly COPD and asthma. Pontus Andell *et al.,* [19] supports using ticagrelor in ACS patients with COPD especially that they've experienced higher rates of ischemic events compared to non-COPD patients. However, the study also revealed that ticagrelor is associated with higher discontinuation rate due to dyspnea in COPD than in non-COPD patients (2.5% vs. 0.9%%; interaction P-value= 0.616). The other analysis, Robert F. Storey *et al.,* [20] also showed that drug discontinuation due to dyspnea was higher with ticagrelor than with clopidogrel (5.9% vs. 1.6%; P=0.0001). Additionally, in both analyses, COPD and asthmatic patients were not at higher risk of developing dyspnea from ticagrelor than others. Data presented from both analyses provides reassurance that COPD is not a precipitating factor for higher dyspnea rate from ticagrelor. However, compliance is a very important aspect that effects the success of every treatment, it could alter outcomes and lead to higher cardiovascular events, thus, it is essential to consider this point carefully when prescribing ticagrelor since it was associated with higher discontinuation rates in the analyses.

Bleeding Risk in Elderly

Three studies were found comparing ticagrelor and clopidogrel's efficacy and risk of bleeding in elderly patient's ≥75 years. The POPULAR-AGE trial included patients who were ≥70 years; this exception was made because the trial met all other inclusion criteria and had only 5 years difference in age. Two of the studies that specified elderly patients have contrarily results, one of them [21] showed significant increased risk of bleeding in elderly with ticagrelor over clopidogrel. The other [22] showed no increased risk of major bleeding with ticagrelor over clopidogrel in elderly. However, they both agreed that ticagrelor and clopidogrel have similar ischemic endpoints in elderly. The third study [23] targeted high bleeding risk (HBR) patients including patient ≥75 years, and it supports the results of the POPULAR-AGE trial were ticagrelor increased the risk of major bleeding when compared to clopidogrel in HBR patients.

DAPT Duration in Elderly

The optimal treatment duration of DAPT remains controversial. Three RCTs included in this review compared different stents with short DAPT durations targeting HBR patients [35-37]. They all agreed that short DAPT as short as 1-month is as safe and effective as 12-month DAPT in HBR and elderly patients. Ticagrelor monotherapy after short-term DAPT may improve ischemic and bleeding risks in ACS patients, because its strategy is less potent than ticagrelor-based DAPT but more potent than aspirin or clopidogrel monotherapy.

Three subgroup analyses were included comparing short DAPT versus long DAPT [38-40]. Two analysis support the use of 1-month DAPT over 12-month DAPT [39, 40]. Similar results were shown in the third analysis [40] but it was comparing 6-months DAPT versus 24-months DAPT and found that in elderly patients DAPT beyond 6-months increased the risk of bleeding, without significantly preventing ischemic outcomes.

Two ongoing RCTs were included [41, 42] and are expected to provide guidance for the management of DAPT duration in elderly patients. One of them is comparing 1-month versus 12-month DAPT in high bleeding risk patients including patient's ≥ 75 years of age [41]. And the other discontinued the P2Y12-inhibitor antiplatelet and continued aspirin monotherapy after 3-months of DAPT for patients free from ischemic events [42].

This review shows that in elderly patients a short-term DAPT could be beneficial in reducing the risk of bleeding without increasing the ischemic risk.

Overall, this review highlights an important point that elderly patients and patients with respiratory conditions are significantly underestimated in the literature. Future studies should focus more on providing details regarding the safety and efficacy of ticagrelor and other P2Y12-inhibitors in DAPT regimens specifically in elderly patients and patients with respiratory conditions, mostly COPD and asthma. However, a regimen that balances ischemic and bleeding risks that fits all patients is inapplicable. Therefore, DAPT therapy should be individualized by adjusting treatment on a patient-by-patient method and weighting each individual's ischemic and bleeding or dyspnea risks.

Strength and Limitations

A systematic and careful search strategy that retrieves several articles to answer the research questions was performed in this scooping review. A couple of common electronic databases were used as primary sources. All parts of the PICOS framework were searched with various keywords in order to target all relevant studies.

An assessment of the quality of the included studies was not performed since scoping reviews are not deliberated to evaluate the quality of the included studies. Consequently, the conclusion of this review is not based on the intrinsic quality of the studies included, but on their existence in the literature.

Additionally, studies published in languages other than English were excluded, potentially leading to language bias and exclusion of related articles published in other languages. Also, prasugrel wasn't included in this review due to it not being recommended for elderly patient's ≥75 years and not being commonly used. Although there is a general agreement that elderly patients are defined by ≥75 years, ageing is a continuous process and the cut-off of 75 years remains arbitrary.

CONCLUSION

This scooping review of the available literature suggests that dyspnea from ticagrelor has mostly mild to moderate intensity and that COPD and asthmatic patients are not at higher risk of dyspnea from ticagrelor. Even though COPD patients might benefit more from ticagrelor since they are at higher risk of ischemic events, it is also associated with higher discontinuation rate due to dyspnea than in non-COPD patients.

Data suggests there is no difference between clopidogrel and ticagrelor in elderly patients in regard to cardiovascular endpoint while some studies suggest that clopidogrel might lower the risk of bleeding. Also, elderly patients might benefit from a shorter duration of DAPT to minimize their higher risk of bleeding. However, data regarding DAPT in elderly and respiratory disease patients is limited, and evidence regarding the most appropriate regimen for them remains inconclusive. Therefore, DAPT therapy should be individualized by taking into account individual ischemic and bleeding risk factors.

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