Stroke

CLINICAL AND POPULATION SCIENCES

Divergence Between Clinical Trial Evidence and Actual Practice in Use of Dual Antiplatelet Therapy After Transient Ischemic Attack and Minor Stroke

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BACKGROUND: Randomized controlled trials (RCTs) proved that short-term (21–90 days) dual antiplatelet therapy (DAPT) reduces the risk of early ischemic recurrences after a noncardioembolic minor stroke or high-risk transient ischemic attack (TIA) without substantially increasing the hemorrhagic risk. We aimed at understanding whether and how real-world use of DAPT differs from RCTs.

METHODS: READAPT (Real-Life Study on Short-Term Dual Antiplatelet Treatment in Patients With Ischemic Stroke or TIA) is a prospective cohort study including >18-year-old patients treated with DAPT after a noncardioembolic minor ischemic stroke or high-risk TIA from 51 Italian centers. The study comprises a 90-day follow-up from symptom onset. In the present work, we reported descriptive statistics of baseline data of patients recruited up to July 31, 2022, and proportions of patients who would have been excluded from RCTs. We compared categorical data through the χ^2 test.

RESULTS: We evaluated 1070 patients, who had 72 (interquartile range, 62–79) years median age, were mostly Caucasian (1045; 97.7%), and were men (711; 66.4%). Among the 726 (67.9%) patients with ischemic stroke, 226 (31.1%) did not meet the RCT inclusion criteria because of National Institutes of Health Stroke Scale score >3 and 50 (6.9%) because of National Institutes of Health Stroke Scale score >5. Among the 344 (32.1%) patients with TIA, 69 (19.7%) did not meet the RCT criteria because of age, blood pressure, clinical features, duration of TIA, presence of diabetes score <4 and 252 (74.7%) because of age, blood pressure, clinical features, duration of TIA, presence of diabetes score <6 and no symptomatic arterial stenosis. Additionally, 144 (13.5%) patients would have been excluded because of revascularization procedures. Three hundred forty-five patients (32.2%) did not follow the RCT procedures because of late (>24 hours) DAPT initiation; 776 (72.5%) and 676 (63.2%) patients did not take loading doses of aspirin and clopidogrel, respectively. Overall, 84 (7.8%) patients met the RCT inclusion/exclusion criteria.

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CONCLUSIONS: The real-world use of DAPT is broader than RCTs. Most patients did not meet the RCT criteria because of the severity of ischemic stroke, lower risk of TIA, late DAPT start, or lack of antiplatelet loading dose.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT05476081.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: aspirin ■ clopidogrel ■ follow-up studies ■ prospective studies ■ ticagrelor

Nonstandard Abbreviations and Acronyms

ABCD²	age, blood pressure, clinical features, duration of transient ischemic attack, presence of diabetes
CHANCE	Clopidogrel in High-Risk Patients With Acute Non-Disabling Cerebrovascular Events
DAPT	dual antiplatelet therapy
ISA-AII	Italian Stroke Association-Associazione Italiana Ictus
IVT	intravenous thrombolysis
NIHSS	National Institutes of Health Stroke Scale
POINT	Platelet Oriented Inhibition in New Transient Ischemic Attack and Minor Ischemic Stroke
RCT	randomized controlled trial
READAPT	Real-Life Study on Short-Term Dual Antiplatelet Treatment in Patients With Ischemic Stroke or Transient Ischemic Attack
RWS	real-world settings
THALES	The Acute Stroke or Transient Ischemic Attack Treated With Ticagrelor and Acetylsalicylic Acid for Prevention of Stroke and Death
TIA	transient ischemic attack
TOAST	Trial of ORG 10172 in Acute Stroke Treatment

Stroke recurrence after minor ischemic stroke or transient ischemic attack (TIA) is up to 5% in the first 3 months after the index event.[1,2] Preventing ischemic recurrences is the key goal of stroke care. International guidelines[3–8] recommend a short-term—from 21 to 90 days—dual antiplatelet therapy (DAPT) with aspirin and clopidogrel or ticagrelor for secondary prevention of a noncardioembolic minor ischemic stroke or high-risk TIA. These recommendations are based on the results of 3 randomized controlled trials (RCTs): the CHANCE trial (Clopidogrel in High-Risk Patients With Acute Non-Disabling Cerebrovascular Events),[9] the POINT trial (Platelet Oriented Inhibition in New TIA and Minor Ischemic Stroke),[10] and the THALES trial (The Acute Stroke or TIA Treated With Ticagrelor and Acetylsalicylic Acid for Prevention of Stroke and Death).[11] In RCTs, the reduction of the risk of ischemic recurrences outweighed the hemorrhagic risk, which kept equal or slight above single antiplatelet therapy. The definition of the index events differs across RCTs: minor stroke was defined by a National Institutes of Health Stroke Scale (NIHSS) score ≤3 in CHANCE and POINT and ≤5 in THALES, whereas a high-risk TIA was defined by an age, blood pressure, clinical features, duration of TIA, presence of diabetes (ABCD²) score ≥4 in CHANCE and POINT and 6 in THALES. All RCTs excluded patients treated with acute revascularization procedures (thrombolysis, endovascular treatment, or thrombectomy). Moreover, patients started DAPT within 24 hours from symptom onset and received a variable initial dose of aspirin (50–325 mg) together with clopidogrel (300–600 mg) or ticagrelor (180 mg) loading dose.

The effectiveness of DAPT could differ in real-world settings (RWS), where patients might not meet the RCT inclusion/exclusion criteria or follow strict trial procedures on time to DAPT start and antiplatelet loading doses.

The READAPT trial (Real-Life Study on Short-Term Dual Antiplatelet Treatment in Patients With Ischemic Stroke or TIA) is an ongoing prospective, multicenter, observational study including patients treated with short-term DAPT in stroke secondary prevention. The primary aim of READAPT is to describe the benefits and risks of DAPT in RWS. The aim of this analysis is to evaluate to what extent patients treated with DAPT in RWS meet the RCT inclusion criteria and follow their procedures.

METHODS

Study Design, Participants, and Setting

READAPT (NCT05476081) is an observational, prospective, multicenter, real-world study, which includes a baseline observation (ie, index event) and a 90-day follow-up; it was coordinated by the University of L'Aquila and endorsed by ISA-AII (Italian Stroke Association-Associazione Italiana Ictus). The study followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[12] The Internal Review Board of the University of L'Aquila cleared

the study with the number 03/2021 in February 2021, and the local ethic committees of each participating center subsequently approved it. All included patients or their proxies had to sign an informed consent.

Since February 2021, 51 Italian centers (Table S1) have actively enrolled all consecutive patients treated with DAPT. While the study is still ongoing, the present analysis is based on baseline data of all patients recruited up to July 31, 2022 (database READAPT-1). The database is available upon request to the corresponding author.

Inclusion and Exclusion Criteria

The READAPT study included patients both hospitalized or not with acute noncardioembolic mild or moderate ischemic stroke or high-risk TIA, aged >18 years, and treated with a short course of DAPT. Ischemic strokes were distinguished from TIAs according to the World Health Organization time-based criterion: events were defined as TIAs if symptoms lasted <24 hours and as ischemic strokes when symptoms lasted ≥24 hours regardless of the presence of brain lesions at neuroimaging. Local investigators were responsible for diagnostic accuracy and exclusion of mimics. Due to the observational design of the study and the variability of minor stroke and high-risk TIA definitions in literature, we did not establish strict inclusion and exclusion criteria such as NIHSS and ABCD^2 cutoff scores, but we recommended the adherence to guidelines.[3–8]

We excluded patients either receiving DAPT after endovascular stenting procedures, already randomized to interventional RCTs on stroke prevention, or with conditions affecting the compliance to study procedures or data reliability.

Study Procedures, Data Collection, and Variables

Before the recruitment started, all centers received an update on RCT state-of-the-art and guidelines on DAPT for minor ischemic stroke and high-risk TIA. We held online education sessions summarizing RCT designs and results and national and international guideline recommendations on DAPT; we focused on high-risk TIA and minor stroke definition and DAPT dose and duration.[3–8] We further trained participants on study procedures and on the use of electronic case report forms.

Physicians chose DAPT regimen—loading dose and treatment duration—and the antiplatelet to be continued after DAPT discontinuation according to the best clinical practice. During the study period, ticagrelor was not licensed for stroke by the Italian regulatory agency for drug supervision (Agenzia Italiana del Farmaco).[13] We encouraged a 21- to 30-day course of DAPT, which could be extended up to 90 days upon RCT evidence and guidelines.[3–8] According to RCTs, we defined DAPT loading dose as aspirin 300 mg or clopidogrel 300 to 600 mg. The loading dose was administered on day 1 of DAPT and was followed by aspirin 100 mg daily together with clopidogrel 75 mg daily for the remaining DAPT period.

A baseline case report form was used to collect patients' demographics, vascular risk factors, pre-event treatment, NIHSS score, ABCD^2 score, pre- and post-event modified Rankin Scale, time to DAPT start, treatment regimen, concurrent treatments, neuroimaging characteristics, cause of the index event according to the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) classification, and acute treatment (ie, thrombolysis, thrombectomy, endarterectomy).

Data were entered in an electronic anonymized database created using the Research Electronic Data Capture software[14,15] hosted at the University of L'Aquila and accessed through link/password or a quick response (QR) code. The study staff remotely monitored the centers, encouraged patients' recruitment, and periodically sent newsletters on study progresses. Quality check was done on a weekly basis, and queries were regularly sent to centers to ensure the integrity of data and completeness of the follow-up. We rejected cases with either incomplete or incorrect data in the following mandatory variables: "age," "NIHSS," "ABCD^2," "thrombolysis," "thrombectomy," "endarterectomy," "aspirin loading dose," "clopidogrel loading dose," "time to DAPT start," "mRS," "previous intracranial hemorrhage," and "procedure-related index event." The investigators of the leading center—University of L'Aquila—had full access to all the data and take responsibility for its integrity and data analysis.

Statistical Analysis

We reported descriptive statistics about demographics, characteristics of the index event, and reasons for exclusion from RCTs, namely NIHSS, ABCD^2 score, antiplatelet loading doses, time to DAPT start, intravenous thrombolysis (IVT), thrombectomy, endarterectomy, modified Rankin Scale, procedure-related events, stroke isolated symptoms, and history of intracranial hemorrhage (Table S2). We excluded from the analysis patients receiving DAPT with aspirin and ticagrelor as their low number could have affected the homogeneity of our cohort.

We reported proportions and numbers of READAPT patients who did not meet the RCT inclusion criteria and follow their procedures. We considered THALES despite its different treatment regimen (ie, aspirin and ticagrelor) as we did indirect comparisons between our and RCT cohorts. Moreover, we did not evaluate efficacy outcomes, which might be affected by

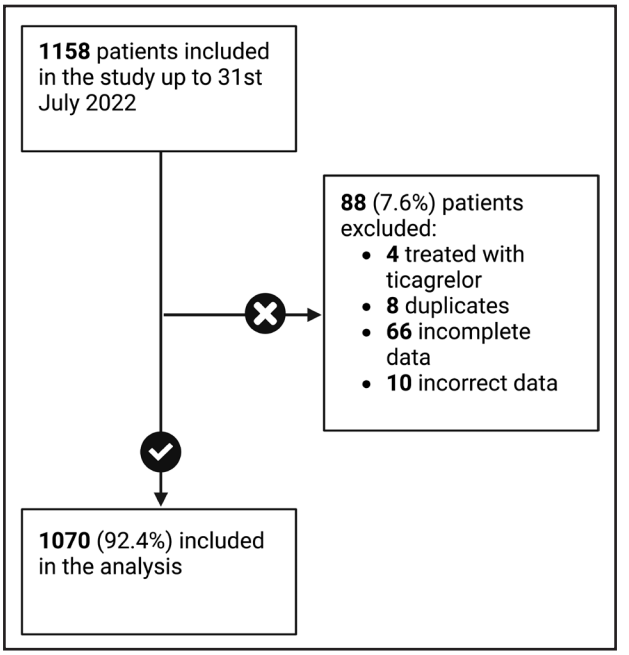

Figure 1. Flowchart that summarizes the reasons for exclusion from the analysis.

the DAPT regimen. However, we did not consider CHANCE-II inclusion criteria, which included only patients with CYP2C19 (cytochrome P450 2C19) loss-of-function alleles.[16]

Categorical data were reported as number and percentage, whereas continuous data were reported as median and interquartile range. We compared categorical data through the χ^2 test. Statistics were performed through SPSS, version 20 (IBM Corp, Armonk, NY).

Ethics Statement

This study was approved by the Internal Review Board of the University of L'Aquila (Italy), and patients gave written informed consent according to the Declaration of Helsinki.

RESULTS

Between February 2021 and July 2022, 1158 patients were enrolled: 8 (0.7%) were duplicates, 76 (6.5%) had missing or incorrect data, and 4 (0.3%) were excluded because they were treated with ticagrelor and aspirin; thus, 1070 (92.4%) were included in the analysis (Figure 1). Median age was 72 (interquartile range, 62–79) years, 1045 (97.7%) patients were Caucasian, and 711 (66.4%) were men. Four hundred fifty-nine patients (42.9%) were already on treatment with single antiplatelet therapy (ie, aspirin or clopidogrel); 190 (41.4%) of them did not report any cardiac, cerebrovascular,

Table. Baseline Characteristics of Patients Included in READAPT, CHANCE, POINT, and THALES RCTs

Baseline characteristics*	READAPT	CHANCE	POINT	THALES
n (intervention group for RCTs)	1070	2584	2432	5523
Median (IQR) or mean (±SD) age, y	72 (62–79)	63 (55–72)	65.0 (55–74)	65.2±11.0
Men, n (%)	711 (66.4)	1732 (67.0)	1.335 (54.9)	3.415 (61.8)
Race, n (%)				
Caucasian	1045 (97.7)	0 (0)	1774 (75.2)*	2973 (53.8)
Black	8 (0.7)	0 (0)	473 (20.0)	21 (0.4)
Asian	9 (0.8)	2584 (100.0)	77 (3.3)	2353 (42.6)
Other	8 (0.7)	0 (0)	180 (7.7)	176 (3.2)
BMI, kg/m^2; median (IQR)	26 (24–28)	25 (23–26)	NA	25.9 (23.3–29.0)
Systolic blood pressure, mm Hg; median (IQR)	150 (137.2–170)†	150 (136–161)	159.0 (143.0–180.0)	150.0 (135.0–163.0)
Diastolic blood pressure, mm Hg; median (IQR)	83 (75–90)†	90 (80–98)	87.0 (77.0–98.0)	84.0 (79.0–91.0)
Medical history				
Arterial hypertension, n (%)	835 (78)	1716 (66.4)	1693 (69.9)	4298 (77.8)
Hypercholesterolemia, n (%)	615 (57.5)	290 (11.2)	NA	NA
Diabetes, n (%)	306 (28.6)	550 (21.3)	678 (28.0)	1589 (28.8)
Current or previous smoking, n (%)	454 (42.4)	1116 (43.2)	496 (20.4), current	1504 (27.2), current
Congestive heart failure, n (%)	26 (2.4)	42 (1.6)	64 (2.6)	NA
Myocardial infarction, n (%)	103 (9.6)	43 (1.7)	257 (10.6)	NA
Ischemic stroke, n (%)	111 (10.4)	516 (20.0)	NA	901 (16.3)
TIA, n (%)	85 (7.9)	94 (3.6)	NA	275 (5.0)
ICH, n (%)	8 (0.7)	NA	NA	NA
Previous medication use				
Taking aspirin at presentation, n (%)	390 (36.4)	279 (10.8)	1417 (58.3)	754 (13.7)
Taking clopidogrel at presentation, n (%)	69 (6.4)	10 (0.4)	48 (2.0)	75 (1.4)
Type of index event (time based)				
TIA, n (%)	344 (32.1)	717 (27.7)	1056 (43.4)	491 (8.9)
Ischemic stroke, n (%)	726 (67.9)	1867 (72.3)	1376 (56.6)	5032 (91.1)
NIHSS score at onset in patients with stroke, median (IQR)	2.00 (3.0–4.0)	NA	2.0 (1.0–2.0)	NA
ABCD^2 score in patients with TIA, median (IQR) or (%)	4 (4.0–5.0); ≤5: 280 (81.4); >5: 64 (18.6)	4 (4.0–5.0)	5.0 (4.0–6.0)	≤5: 60 (1.1); >5: 431 (7.8)

ABCD^2 indicates age, blood pressure, clinical features, duration of transient ischemic attack, presence of diabetes; BMI, body mass index; CHANCE, Clopidogrel in High-Risk Patients With Acute Non-Disabling Cerebrovascular Events; ICH, intracranial hemorrhage; IQR, interquartile range; NA, not available; NIHSS, National Institutes of Health Stroke Scale; POINT, Platelet Oriented Inhibition in New Transient Ischemic Attack and Minor Ischemic Stroke; RCT, randomized controlled trial; READAPT, Real-Life Study on Short-Term Dual Antiplatelet Treatment in Patients With Ischemic Stroke or Transient Ischemic Attack; THALES, The Acute Stroke or Transient Ischemic Attack Treated With Ticagrelor and Acetylsalicylic Acid for Prevention of Stroke and Death; and TIA, transient ischemic attack.

*In the POINT trial, the Hispanic ethnic group was assessed only in patients in the United States (added to other category).

†992 evaluable cases.

or peripheral artery diseases in their medical history. Among the 323 patients (30.2%) with prior condition requiring ischemic secondary prevention, 269 (83.2%) were already on single antiplatelet therapy. According to the 24-hour cutoff for symptom duration, 726 (67.9%) patients had an ischemic stroke and 344 (32.1%) a TIA. The Table reports all the baseline characteristics of patients included in the READAPT compared with CHANCE, POINT, and THALES.

At baseline, 226 (31.1%) patients with ischemic stroke had an NIHSS score >3, which was CHANCE and POINT stroke severity cutoff; and 50 (6.9%) had an NIHSS score >5, which was THALES cutoff. Seventy-nine (19.7%) patients with TIA had ABCD^2 score <4 and 257 (74.7%) had ABCD^2 score <6 and no symptomatic arterial stenosis (ie, intracranial or internal carotid stenosis); thus, outside RCT definitions of high-risk TIAs. Eleven (1%) patients were <40 years, thus, not matching the CHANCE and THALES inclusion criteria (Figure S1). One hundred forty-four (13.5%) patients treated with DAPT in RWS would have been excluded from RCTs because of IVT, endovascular treatment (7 [0.6%]), or urgent carotid endarterectomy (30 [2.8%]). Two hundred fifty-five (23.8%) patients reported at least 1 exclusion criteria among NIHSS score >5/ABCD^2 score <4 and revascularization procedures, whereas 38 (3.6%) reported >1 of these exclusion criteria (Figure 2). Moreover, 39 (3.68%) patients had a modified Rankin Scale score >2, 5 (0.5%) patients had a procedure-related ischemic event, and 38 (3.5%) had isolated sensory visual or dizziness symptoms without lesion at neuroimaging, which were CHANCE exclusion criteria; 8 (0.7%) patients had a history of intracerebral hemorrhage, which was an exclusion criterion of all RCTs (Figure 2).

Regarding DAPT start, late initiation (>24 hours) was reported in 345 (32.2%) patients. In detail, 189 cases (17.6%) started DAPT within 25 to 48 hours and 156 (14.6%) >48 hours (Figure 3). Overall, 776 (72.5%) did not receive an aspirin loading dose; 316 (40.7%) of them were already on treatment with aspirin. Additionally, 676 (63.2%) patients did not receive a clopidogrel loading dose; among them, 61 (9.0%) were already on treatment with clopidogrel (Figure S2). Six hundred thirty-three (59.2%) patients did not follow at least 1 RCT procedure because of late DAPT

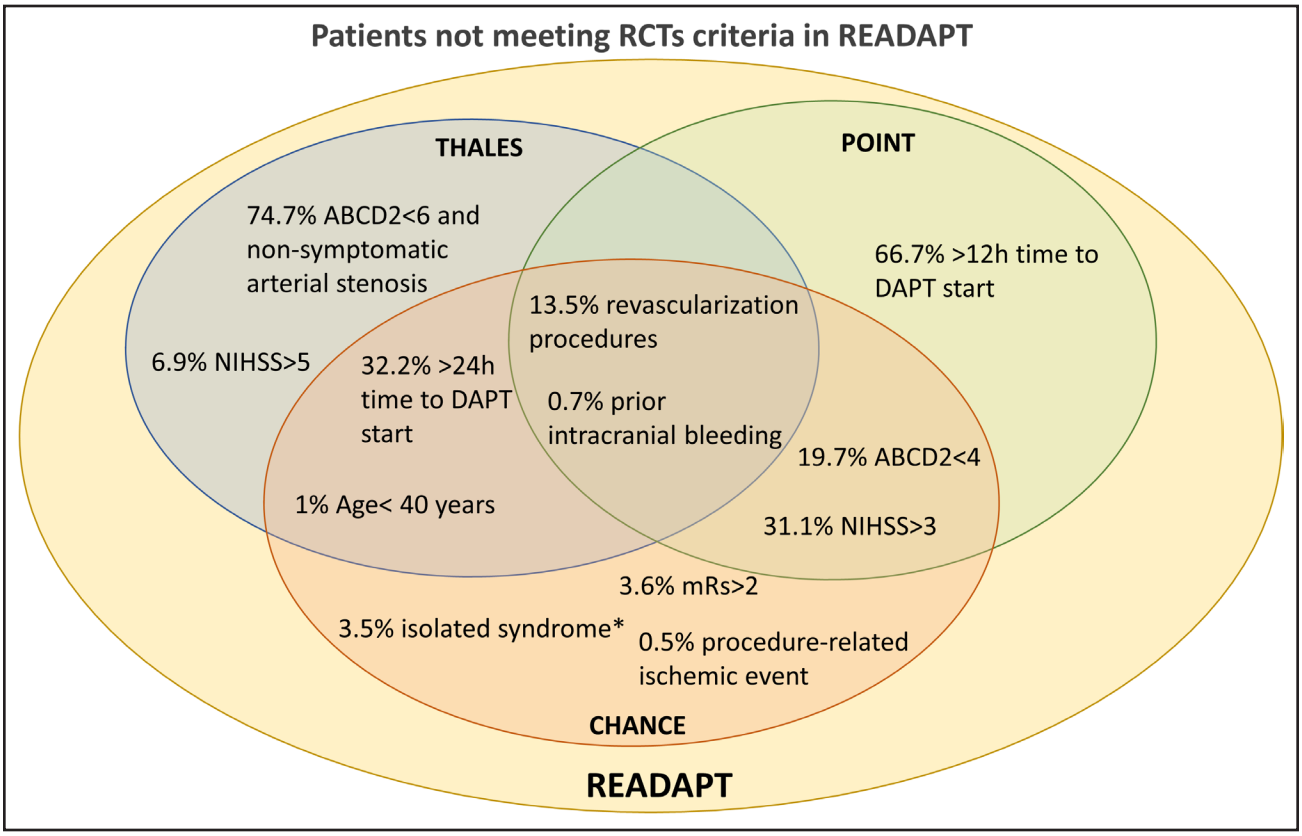

Figure 2. Graphic representation of the READAPT (Real-Life Study on Short-Term Dual Antiplatelet Treatment in Patients With Ischemic Stroke or Transient Ischemic Attack) cohort.

In circles, there are proportions of READAPT patients who do not match the THALES (The Acute Stroke or Transient Ischemic Attack Treated With Ticagrelor and Acetylsalicylic Acid for Prevention of Stroke and Death), POINT (Platelet Oriented Inhibition in New Transient Ischemic Attack and Minor Ischemic Stroke), and CHANCE (Clopidogrel in High-Risk Patients With Acute Non-Disabling Cerebrovascular Events) inclusion criteria and procedures. ABCD^2 indicates age, blood pressure, clinical features, duration of transient ischemic attack, presence of diabetes; DAPT, dual antiplatelet therapy; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and RCT, randomized controlled trial.
*Isolated sensory, visual, or dizziness/vertigo syndrome without an ischemic lesion at neuroimaging.

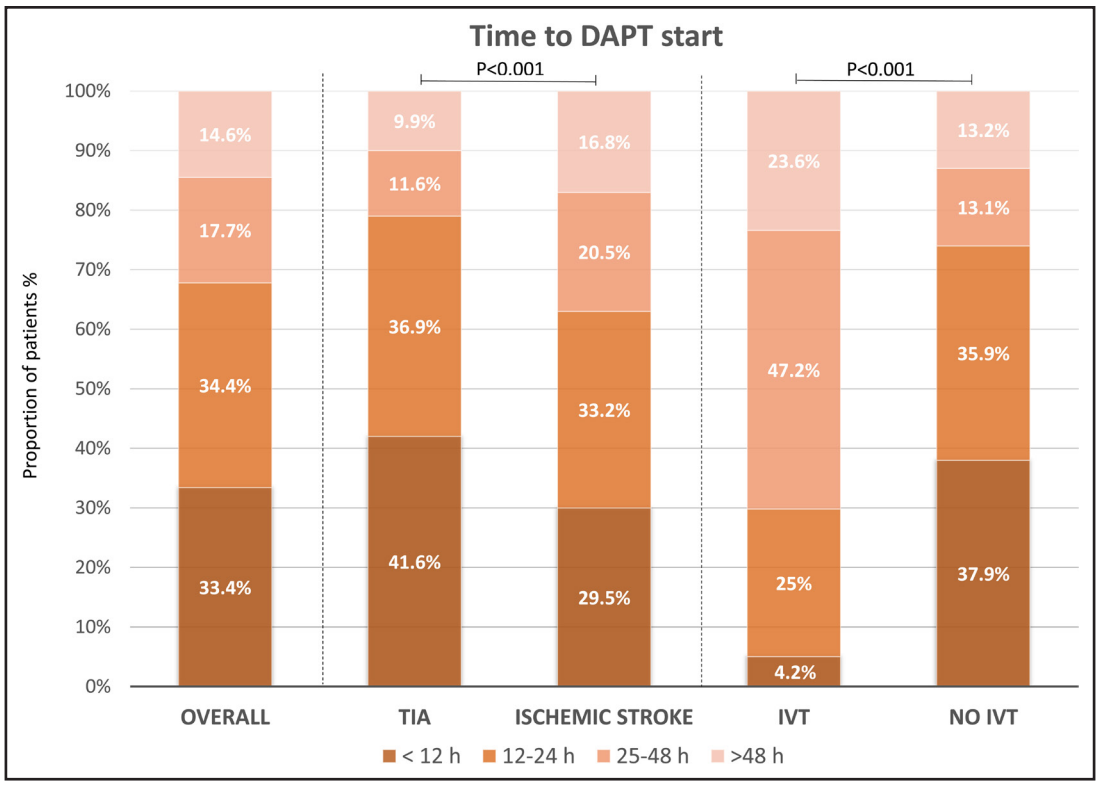

Figure 3. Proportion of patients starting dual antiplatelet therapy (DAPT) within 12 h, 12 to 24 h, 25 to 48 h, or after 48 h from symptom onset in the overall study cohort (n=1070), those with a transient ischemic attack (TIA; n=344), those with an ischemic stroke (n=726), and those treated (n=144) or not (n=926) with intravenous thrombolysis (IVT).

start or lack of either aspirin or clopidogrel loading dose, and 214 (20%) patients did not follow both the procedures. A significantly higher proportion of patients with TIA had a <24-hour time to DAPT start compared with patients with an ischemic stroke (270 [78.5%] versus 455 [62.7%]; *P*<0.0001; Figure 3) and more frequently received a clopidogrel loading dose (145 [42.2%] compared with 249 [34.3%]; *P*=0.012; Figure 3). Conversely, a greater proportion of patients treated with IVT had a >24-hour time to DAPT start compared with those not treated with IVT (102 [70.8%] versus 243 [26.2%]; *P*<0.0001; Figure 3) and less frequently received aspirin (19 [13.2%] versus 274 [29.6%]; *P*<0.001) and clopidogrel loading doses (31 [21.5%] versus 363 [39.2%]; *P*<0.0001; Figure 4).

Overall, only 92 (8.6%) patients would have met all RCT criteria and followed their procedures: 586 (54.7%) did not qualify for CHANCE, 811 (75.8%) for POINT, and 798 (74.5%) for THALES (Figure 5).

DISCUSSION

This analysis of the READAPT study cohort showed that most patients treated with DAPT in secondary prevention of minor stroke or high-risk TIA in RWS do not meet the strict RCT inclusion/exclusion criteria and follow their procedures. Among the RCTs, POINT had the stricter inclusion criteria with two-thirds of READAPT patients not matching the RCT population mainly because of >12-hour time to DAPT start from symptom onset.[10] RCTs represent the gold standard of medical evidence to assess the efficacy and safety of new therapeutic interventions. However, RCT results are not always generalizable outside the experimental setting; thus, RWS studies might complement RCTs to guide best medical treatment.[17]

Some demographics of the READAPT cohort remarkably differ from RCTs. Patients included in our study were older and more often reported comorbidities such as hypercholesterolemia or hypertension (Table). Most of our patients were Caucasian, different from CHANCE, where almost the entire sample was Asian, and from POINT and THALES, where other ethnic groups were represented. The reduced representation of ethnicities might be due to the setting of READAPT restricted to Italy, where ethnic differences are limited.[18] All RCTs and READAPT registered a low proportion of women, which ranged between 33% and 45%. The prevalence of ischemic strokes is higher among women according to the Global Disease Burden,[19] but several factors might underlie sex differences in the aforementioned studies: the low prevalence of noncardioembolic strokes,[20] the higher severity of ischemic stroke in women compared with men precluding DAPT prescription,[21] and disparities between sex in acute management and secondary prevention of ischemic strokes.[22,23]

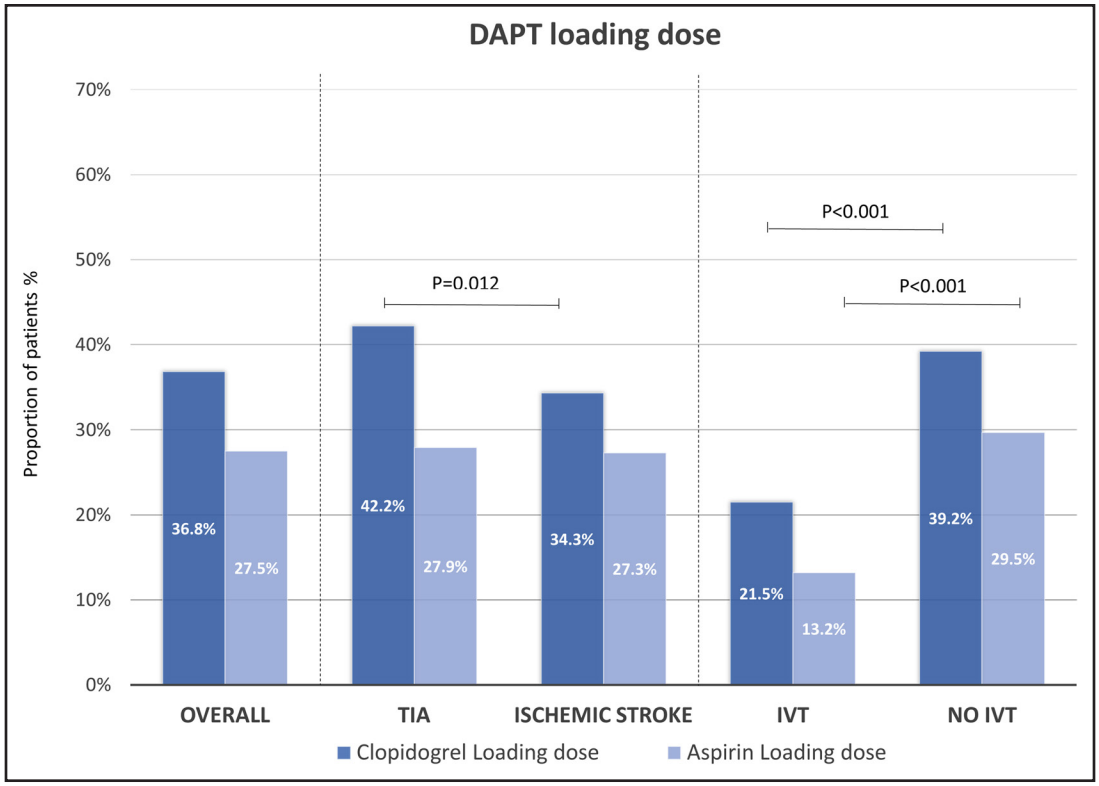

Figure 4. Proportion of patients who received clopidogrel and aspirin loading doses among the entire study population (n=1070), those with a transient ischemic attack (TIA; n=344), those with an ischemic stroke (n=726), and those treated (n=144) or not (n=926) with intravenous thrombolysis (IVT).
DAPT indicates dual antiplatelet therapy.

In our cohort, the median NIHSS score was higher than in POINT and CHANCE trials, which set an NIHSS cutoff of 3, whereas one-third of patients with ischemic stroke had an NIHSS score between 3 and 5 similarly to THALES, which set an NIHSS cutoff of 5. Stroke severity was greater in RWS, where physicians could evaluate patients and prescribe DAPT even after 24 hours from symptom onset and after neuroimaging or further diagnostic examinations (ie, patients with small ischemic lesions and NIHSS score >5, without signs of hemorrhagic infarctions, or with conditions that might benefit from DAPT such as symptomatic intracranial stenosis). Heterogeneity of the READAPT data might justify differences in stroke severity among RWS and RCTs, where all patients had to start treatment within 12 to 24 hours from symptom onset regardless of neuroimaging. Moreover, the NIHSS scale has some limitations; it highly correlates to left middle cerebral artery territory size infarct but underestimates right or posterior circulation strokes.[24–26] A study including patients with minor strokes showed that some components of the NIHSS scale were associated with greater ischemic lesion volume such as neglect, language, and visual field.[27] In RWS there might be patients with low NIHSS score and large ischemic lesions in noneloquent areas or in areas underestimated by the standard NIHSS scale. We need further evidence to correlate stroke severity with ischemic lesion volume, which will be one of the aims of future READAPT analyses. About 20% of patients with TIA in READAPT had an ABCD^2 score <4. In RWS, physicians might prescribe DAPT to patients with lower risk TIA independently from ABCD^2 score because of other coexisting vascular risk factors or atherothrombotic genesis of the ischemic event (ie, symptomatic intracranial stenosis, significant or unstable atherosclerotic plaques) or because already on single antiplatelet treatment.

Differently from all the RCTs, our study included a considerable proportion (19.5%) of patients treated with revascularization procedures, most commonly IVT. Recent guidelines recommend IVT in patients with minor stroke with disabling symptoms,[5,7,8,28] but there is preliminary and limited evidence on the safety of DAPT after IVT. Two observational studies and a case report suggested that hemorrhagic infarctions and minor systemic bleedings were similar between those receiving 21-day DAPT or single antiplatelet treatment at 90 days after IVT or patient discharge, while functional outcome was significantly better in those treated with DAPT.[29–31] However, both the observational studies were retrospective, included limited sample size (ie, about 200 patients), and were restricted to Asian countries.[29,30] Furthermore, none included patients with an NIHSS score >5 and treated with antiplatelet loading doses,[29,30] thus, not evaluating the safety/efficacy ratio in these subsets

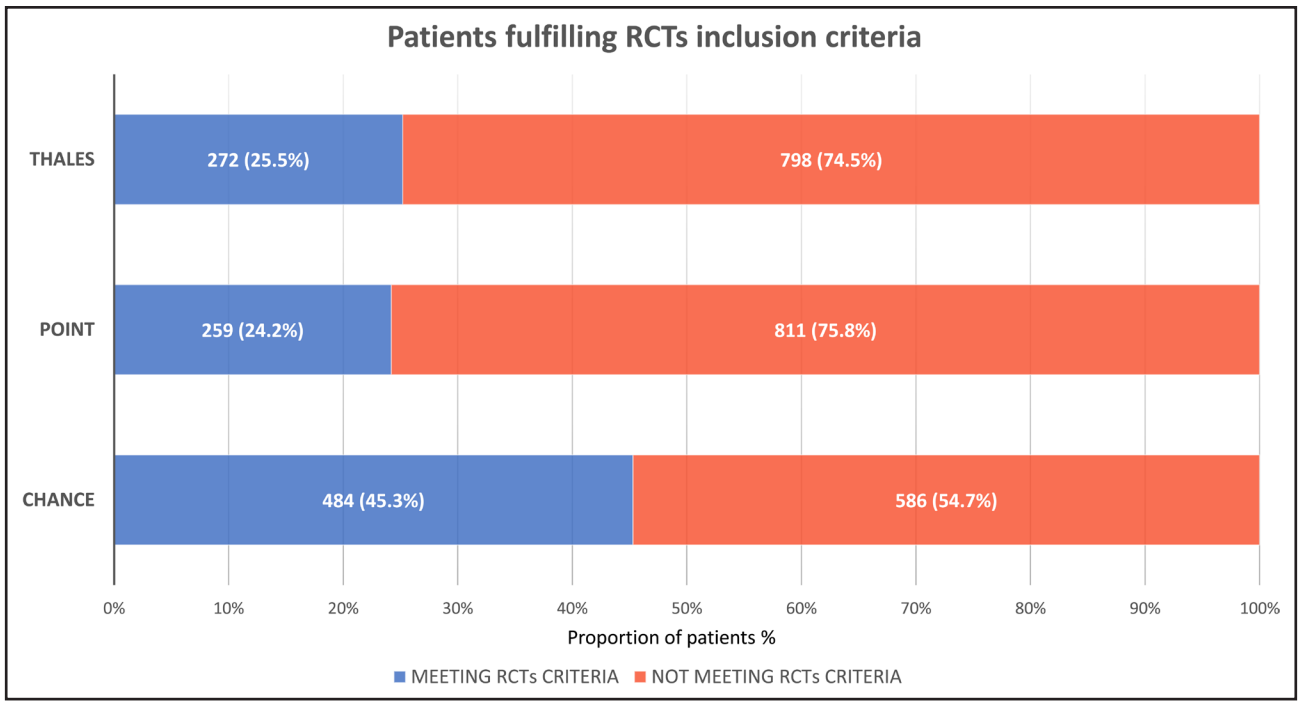

Figure 5. Proportion of patients who matched all inclusion criteria and procedures or had at least one of the randomized controlled trial (RCT) exclusion criteria.

Inclusion criteria of THALES (The Acute Stroke or Transient Ischemic Attack Treated With Ticagrelor and Acetylsalicylic Acid for Prevention of Stroke and Death): National Institutes of Health Stroke Scale (NIHSS) score ≤5, age, blood pressure, clinical features, duration of transient ischemic attack, presence of diabetes (ABCD^2) score ≥6 or with symptomatic intracranial stenosis/>50% carotid arterial stenosis, age ≥40 y; CHANCE (Clopidogrel in High-Risk Patients With Acute Non-Disabling Cerebrovascular Events): NIHSS score ≤3, ABCD^2 score ≥3; age ≥40 y, 24-h time to dual antiplatelet therapy (DAPT) start; and POINT (Platelet Oriented Inhibition in New Transient Ischemic Attack and Minor Ischemic Stroke): NIHSS score ≤3, ABCD^2 score ≥4, age ≥18 y, 12-h time to DAPT start. For exclusion criteria, refer to Figure 2 (n=1070).

of patients, who might be at higher risk of systemic or intracranial bleedings.

Most patients did not follow the RCT procedures requiring maximum 24-hour time to DAPT start and antiplatelet loading dose. One-third of patients started DAPT after 24 hours, which was the maximum time to DAPT start in CHANCE and THALES, possibly due to delays in the first medical evaluation. Patients with mild or transient symptoms might underestimate the problem, wait for spontaneous remission of deficits, and, thus, seek medical attention after the 24-hour window of RCTs. Additionally, patients with ischemic stroke started DAPT later than those with a TIA due to acute revascularization procedures or possible concerns on hemorrhagic infarction. Although the RCT subgroup analyses and a recent meta-analysis proved that a <12-hour DAPT start maximizes treatment risks/benefits,[32–34] DAPT proved still beneficial within 72 hours from symptom onset.[34] READAPT follow-up data will clarify the effectiveness and safety of DAPT in patients starting treatment after 24 hours. RCTs administered a variable dose of 300 to 325 mg aspirin and 300 to 600 mg clopidogrel irrespective of prior antiplatelet treatments. An antiplatelet loading dose within 48 hours from symptom onset has been accepted in acute ischemic stroke management since the results of 2 main RCTs,[35,36] which confirmed the clinical efficacy of this therapeutic scheme based on the dose-dependent inhibition of cyclooxygenases. However, whether only patients naive to antiplatelets should be candidates to loading dose is unknown, and heterogeneity of RCT procedures did not allow clear indications on loading dose and DAPT. In our cohort, most patients receiving a loading dose were naive to prior antiplatelets. The lack of clopidogrel loading dose in patients naive to the treatment might be because they were already on treatment with aspirin before the ischemic event or had comorbidities determining a high hemorrhagic risk. Other possible contributing factors might be that neurologists were not familiar with using clopidogrel loading dose or had safety concerns in some subgroups of patients (ie, old patients, those treated with IVT or with cerebral small vessel disease).

The READAPT trial adopted rigorous procedures to ensure accuracy and quality of the collected data such as the use of specific electronic case report forms to retain key information in homogenous and standardized fashion. Indeed, electronic health records frequently used in real-world studies contain a high number of data often lacking data quality control. In this analysis, we included only cases with complete data in the variables of interest and reduced to a minimum missing data, which, nevertheless, might have affected the generalizability of results. The Italy-restricted setting and the high

prevalence of Caucasians did not allow to generalize our results to other national and worldwide settings or ethnicities. Additionally, the participating centers did not equally contribute to the study, and the larger contribution of centers in urban areas might have affected our results, which, thus, is not a completely accurate representation of the whole national population. We might have overestimated the number of high-risk TIA as we did not set the strict RCT exclusion criteria on clinical presentation. We did not collect data on those who might have been eligible to DAPT but did not receive it; thus, we could not evaluate possible factors affecting DAPT prescription or changes in DAPT prescription overtime. Lastly, ticagrelor is not licensed for cerebrovascular disease by Agenzia Italiana del Farmaco. Few patients received DAPT with ticagrelor for cardiovascular conditions in comorbidity with the cerebrovascular event and were excluded from the analysis to increase homogeneity of the cohort.

In conclusion, the READAPT study shows that patients treated with DAPT in RWS differ from the RCTs in demographics, disease characteristics, and treatment procedures such as time to treatment start and antiplatelet loading dose. In RWS, physicians also prescribe DAPT to patients with more severe ischemic strokes, low-risk TIA, or treated with revascularization procedures: in these cases, risk/benefits are still uncertain. The READAPT follow-up results will show whether DAPT reduces the risk of ischemic recurrences without increasing the hemorrhagic risk even in the subsets of patients who would have been excluded from RCTs.

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Supplemental Material

Figures S1–S2
Tables S1–S2
Appendix S1

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