Critique on the Use of Early Short-Term Dual Antiplatelet Therapy Following Minor Acute Cerebral Ischemic Events

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Keywords

Acute · Early · Antiplatelet · Aspirin · Clopidogrel · Dual · Ischemia · Hemorrhage

Abstract

Background: Two recent cerebrovascular studies, Clopidogrel (Clo) in High-risk patients with Acute Nondisabling Cerebrovascular Events (CHANCE) and Platelet-Oriented Inhibition in New TIA and minor ischemic stroke (POINT), have purportedly demonstrated the superiority of early dual antiplatelet therapy (DAPT), using aspirin (ASA) plus Clo, in comparison to ASA alone following the occurrence of acute minor cerebral infarction or transient ischemic attack. However, limitations to these trials exist that may not have been adequately explored and presented in the literature, and which may impact the overall efficacy and benefit of DAPT in these situations. Herein we provide a detailed and extensive critique of these 2 trials and of a combined analysis, with particular attention to study data and analyses pertaining to hemorrhagic complications. **Summary:** DAPT may be superior to ASA alone in preventing recurrent cerebral ischemic events, but exclusively during the first 7–10 days of treatment, and probably only in the presence of acute infarction

on cerebral imaging. The impact of minor hemorrhages, which are often clinically consequential and which frequently lead to permanent DAPT discontinuation, has not been adequately considered in the available analyses. Based on data from the trials, DAPT use causes more major and minor hemorrhages than ASA use alone or Clo alone, and Clo use results in fewer hemorrhages than the use of ASA alone. Analyses that include hemorrhage data from the period of Clo alone use as part of the DAPT data may provide inaccurate and erroneous conclusions regarding the relative safety and overall net benefit of DAPT use over ASA alone.

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Introduction

Combination antiplatelet therapy has been a frequent topic of interest and investigation among clinicians treating patients with coronary [1, 2], cerebrovascular and peripheral artery diseases [3]. With regard to cerebrovascular diseases, various combinations of antiplatelet therapies have been considered [3–6] for various mechanisms of ischemia [7–10] and at various time points along the ischemic disease process [11, 12]. Two recent trials, Clop-

Table 1. Results of the major clinical endpoints from the CHANCE and POINT trials

	CHANCE			POINT		
	ASA	ASA + Clo	<i>p</i> value	ASA	ASA + Clo	<i>p</i> value
Cerebral infarction	11.4	7.9	<0.001	6.3	4.6	0.01
Cerebral infarction/hemorrhage	11.7	8.2	<0.001	6.4	4.8	0.01
MI	0.1	0.1	0.69	0.3	0.4	0.46
Composite ischemic outcome*	11.9	8.4	<0.001	6.5	5	0.02
Major/severe hemorrhage	0.2	0.2	0.94	0.4	0.9	0.02
Minor/mild hemorrhage	0.7	1.2	0.12	0.5	1.6	<0.001
Any hemorrhage	1.6	2.3	0.09	N/A		

* Composite outcome of cerebral infarction, MI, or vascular mortality.

Values represent percent event rates for the 2 treatment groups with corresponding *p* values.

N/A, data not available; CHANCE, Clopidogrel in High-risk patients with Acute Nondisabling Cerebrovascular Events; POINT, Platelet-Oriented Inhibition in New TIA and minor ischemic stroke; ASA, aspirin; Clo, Clopidogrel; MI, myocardial infarction.

idogrel (Clo) in High-risk patients with Acute Non-disabling Cerebrovascular Events (CHANCE) and Platelet Oriented Inhibition in New TIA and minor ischemic stroke (POINT), have purportedly demonstrated superiority of dual antiplatelet therapy (DAPT) with aspirin (ASA) plus Clo over ASA alone in preventing recurrent cerebral ischemia, with favorable safety profiles [12, 13]. The purpose of this article is to critically review data from the CHANCE and POINT trials with emphasis on the relative advantages and disadvantages of DAPT with regard to prevention of recurrent cerebral ischemic events and the development of hemorrhagic complications.

Overview of Trials

Both of the trials were large, randomized, placebo-controlled, masked trials that enrolled patients with a minor cerebral ischemic event or transient ischemic attack (TIA) [12, 13]. Minor ischemic events were defined as clinical deficits resulting in an National Institutes of Health Stroke Scale of ≤ 3 in both trials. Exclusion criteria included patients receiving (or scheduled to receive) anticoagulation, thrombolysis, endovascular revascularization, or vascular surgery, those with noninvestigational indications for antiplatelet therapy, and those with contraindications to the use of antiplatelet treatments. In both trials, the baseline characteristics of treatment and control groups were well matched. Predefined primary and safety measures differed between the trials, but both included multiple secondary outcome measures so similar endpoints were assessed.

The CHANCE trial randomized 5,170 patients within 24 h of symptom onset to Clo 300 mg once followed by 75 mg daily for 90 days, plus ASA 75 mg daily for 21 (and not 90) days, or to ASA 75 mg daily plus placebo daily for 90 days [12]. The primary efficacy outcome was any cerebrovascular event (ischemic or hemorrhagic) 90 days after enrollment, and the primary safety outcome was moderate – severe hemorrhage.

The POINT trial randomized 4,881 patients within 12 h of symptom onset to Clo 600 mg once followed by 75 mg daily for 90 days, plus ASA 50–325 mg daily for 90 days, or to ASA 50–325 mg daily plus placebo daily for 90 days [13]. The primary outcome measure was a composite of ischemic vascular events comprising cerebral infarction, myocardial infarction, or ischemic vascular mortality at 90 days. The primary safety outcome was major hemorrhage.

Results of the major endpoints assessed in the 2 trials are listed in the table below (Table 1).

Findings and Limitations

DAPT proved superior to ASA alone for the prevention of recurrent cerebral ischemic events in both the CHANCE (OR 0.67 [95% CI 0.56–0.81]) and POINT trials (OR 0.72 [95% CI 0.56–0.92]), overall and in various patient subgroups [12, 13]. However, certain notable and important exceptions and discrepancies were observed. Whereas DAPT was superior to ASA in patients with TIA and minor deficits in CHANCE [12], subgroup analyses revealed an advantage to DAPT over ASA only in patients

with multiple acute infarcts, and not in those with a single acute infarction or in those with no acute infarction [14]. In POINT, DAPT was superior to ASA only for those with minor clinical deficits but not TIAs, a finding reinforced by the fact that DAPT was superior in patients with acute infarct on imaging, but not in the absence of new infarction [13]. Also notable in POINT was the superiority of DAPT among patients previously on ASA and lack of superiority of DAPT among those not regularly taking ASA prior to the index event [13]. In CHANCE, DAPT was superior to ASA among patients in whom ASA was not taken within 24 h, and not superior among those who had taken ASA within 24 h, but it is unclear if this category implied regular use or nonuse of ASA prior to the presenting index event [12].

General criticisms of the 2 trials have included lack of generalizability, since both included only patients with minor clinical deficits or TIAs [13, 15], and since CHANCE was conducted in East Asia where cerebrovascular profiles differ from American populations in that intracranial atherosclerosis and ICH are more prevalent [12, 15]. An additional critique is the inclusion of a substantial number of TIA patients (35%), which raises uncertainty as to the true nature and possible non-vascular origin of presenting symptoms [13]. The large proportion of TIA patients may have also biased the trials towards less chance for adverse complications in the form of hemorrhagic conversion of the infarction [15]. The unexpected finding of an equal rate of severe hemorrhages among DAPT and ASA groups (0.2 vs. 0.2%, $p=0.94$) in CHANCE also raises questions about the veracity of the data [12].

Hemorrhagic Outcomes

Central to any antithrombotic trial is the relative advantage provided by the treatment agent for the most salient clinical endpoint(s), balanced against potential adverse outcomes. For cerebrovascular trials, prevention of cerebral infarction represents the single most important endpoint, and hemorrhage the greatest risk. As the CHANCE investigators astutely acknowledged, even minor hemorrhages may lead to discontinuation of DAPT in clinical practice, since untreated minor hemorrhages may ultimately become major hemorrhages [16]. In POINT, the investigators defined minor hemorrhages as any nonmajor event that culminates in interruption or discontinuation of treatment [13]. The clinical importance of considering all hemorrhagic outcomes becomes most evident when noting that minor hemorrhages con-

stitute any hemorrhage apart from those most serious cases that are (as defined by the investigators) intracranial and symptomatic, cause hemodynamic compromise, are intraocular and symptomatic, require surgical intervention, receive transfusion therapy, result in hospitalization, or are fatal [12, 13].

As such, “minor” hemorrhages may often be neither trivial nor clinically inconsequential, and may frequently necessitate DAPT cessation, as ultimately evidenced by the 88% permanent treatment discontinuation rate observed in POINT [17]. Thus, an additional major consideration in interpreting the results from CHANCE and POINT involves assessing the overall net benefit of DAPT versus ASA alone by quantifying the advantage observed in preventing recurrent cerebral ischemic events against the dangers incurred in the form of adverse hemorrhagic complications.

CHANCE Data

In a report subsequent to initial trial publication, the CHANCE investigators provided an informative temporal analysis comparing DAPT versus ASA alone for the prevention of cerebral infarctions, and for the risk of any hemorrhage, in tabular and graphic format [16, 18]. Analyses revealed that the benefit of DAPT over ASA in preventing cerebral infarction existed only during the first 8–10 days of treatment, after which the advantage began to approximate, and become negated by, the increased risk of any hemorrhage.

Also evident in the temporal analysis was the finding of a marked imbalance in the timing of major hemorrhages within the DAPT group [18]. Whereas only 1 major hemorrhage occurred during the Clo only period from days 22 to 90, the vast majority (86%) of major hemorrhages occurred during the period of ASA + Clo use from days 1 to 21, with a substantial proportion (43%) occurring during the first week of treatment [18]. Conversely, only 25% of major hemorrhages from ASA occurred during the first 21 days, with the remainder occurring between days 22 and 90. Reinforcing this observation is the finding of substantially more minor hemorrhages in the DAPT group with the use of ASA + Clo compared to when Clo was used alone (83 vs. 17%) [18]. Also notable are the differences in duration of treatment between ASA + Clo and Clo alone (21 vs. 69 days) during which time these imbalances in hemorrhage rates were observed.

POINT Data

In an analogous report, the POINT investigators presented a temporal analysis comparing DAPT and

Table 2. Results of major endpoints from the combined analyses of CHANCE and POINT

	Combined analyses		
	ASA	ASA + Clo	<i>p</i> value
Cerebral infarction	8.9	6.3	<0.001
Cerebral infarction/hemorrhage	9.1	6.5	<0.001
Composite ischemic outcome*	9.1	6.5	<0.001
Ischemic event 0–10 days	7.1	4.7	<0.001
Ischemic event 11–21 days	0.8	0.5	0.22
Major hemorrhage	0.4	0.6	0.12
Major hemorrhage 0–10 days	0.1	0.3	0.18
Minor hemorrhage	0.9	1.9	<0.001
Major or minor hemorrhage	1.3	2.5	<0.001

* Composite outcome of cerebral infarction, MI, or vascular mortality.

Values represent percent event rates for the 2 treatment groups with corresponding *p* values.

CHANCE, Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events; POINT, Platelet-Oriented Inhibition in New TIA and minor ischemic stroke; ASA, aspirin; Clo, Clopidogrel; MI, myocardial infarction.

ASA for the outcomes of major ischemic events and major hemorrhages [19]. Analyses demonstrated an advantage for DAPT over ASA in preventing major ischemic events in the first 7 days of treatment, but not during the 2nd week. A possible advantage for DAPT over ASA was again observed during the 3rd week (statistical analyses on a per week basis not provided). However, during this 3rd week, the rate of major hemorrhages among DAPT users was identical to that of ASA users (in contrast to other time periods) which may have represented a chance finding that spuriously lowered the risk profile of DAPT relative to that of ASA alone. Had the major hemorrhage rate of DAPT resembled that of other analogous time periods, any potential advantage to DAPT over ASA in preventing major ischemic events may have been muted. Also during this 3rd week, the hazard ratio (HR) for major ischemic events among DAPT patients closely approximated that of major hemorrhages, indicating a neutral risk-benefit ratio for DAPT use independent of the ASA comparator group. These facts, plus the lack of benefit during the prior and following weeks, likely negate any advantage to DAPT over ASA during this 3rd week. Minor hemorrhages were not considered in any of the analyses, and no data was presented regarding the outcome of cerebral infarction.

In a separate report, the POINT trial investigators presented an illustrated timeline of all hemorrhages, grouped by anatomic location and treatment, over the entire duration of the trial [17]. Of note is the observation that a substantial preponderance of minor, major, and even fatal hemorrhages occurred during the first 7–10 days of the trial among patients taking DAPT. For major hemorrhages, this finding is numerically corroborated by the negative proportion of hemorrhages, defined as the difference in hemorrhage rates between ASA and DAPT, observed over the same early time period in the previously mentioned temporal analysis report [19]. Visual inspection of the graph provided in the online appendix (eFigure 1) confirms that approximately 50% of all minor hemorrhages among DAPT patients occurred during the first 7–10 days [17], and tabular information from the appendix (eTable 6) reveals that the majority of minor hemorrhages among DAPT patients were cutaneous, gastrointestinal, intracranial, genitourinary, and nasopharyngeal (epistaxis), in nature or origin [17].

Combined Analyses

Recently, a combined analysis of the CHANCE and POINT trials has been published, the main results of which are presented below (Table 2) [20]. In this combined analysis, data for the composite outcome of major ischemic events (myocardial infarction, cerebral infarction, vascular mortality) plus major hemorrhage were presented for the overall duration of the trials (HR 0.74 [95% CI 0.64–0.85]), as was data for the major ischemic event outcome divided into time periods [20]. In the time period analyses, differences between DAPT and ASA were only observed for the 0–10 days period (HR 0.65 [95% CI 0.55–0.77]), in contrast to the 11–21 days (HR 0.72 [95% CI 0.43–1.22]) or the 22–90 days periods (HR 0.94 [95% CI 0.67–1.32]). For the overall analyses, major plus minor hemorrhages were greater in the DAPT group than the ASA alone group (HR 1.88 [95% CI 1.39–2.54]), but no data were presented for all hemorrhages on a time period basis, and no analyses were performed that included all hemorrhages as part of a larger composite outcome along with the major ischemic outcome measure. Finally, no information was provided for the combined outcome of cerebral infarction plus any hemorrhage.

Alternatively, a sensitivity analysis was performed that did incorporate the composite outcome of major ischemic events plus all hemorrhages [20]. Each outcome measure was ascribed a relative clinical value score, with the composite major ischemic outcome representing the comparator measure and ascribed a clinical

cal value score of 1. Major and minor hemorrhages were evaluated over a range of clinical value scores, with major hemorrhage value scores ranging from 0.5 to 1.2, and minor hemorrhage scores ranging from 0.1 to 0.5. Evident in the methodology of the sensitivity analysis is the relative importance ascribed to the ischemic event and major hemorrhage outcome measures, and the diminutive importance ascribed to minor hemorrhage as an outcome measure. No numerical or statistical details pertaining to the sensitivity analyses were provided, and the authors simply stated that the sensitivity analyses “showed similar results” to the main findings.

In a subgroup analysis of the CHANCE data, substantially fewer major hemorrhages occurred in the DAPT group compared to the ASA only group during the latter Clo only period of the trial, from days 22 to 90 (0.04 vs. 0.3%, $p = 0.09$) [20]. Given the overall equivalent rate of major hemorrhages between the DAPT and ASA groups [12], the finding of fewer major hemorrhages in the DAPT group during the time of Clo only use implies a greater rate of major hemorrhages from DAPT during the period of ASA + Clo use from days 1 to 21 (data not presented). This premise is substantiated by review of data presented in the CHANCE temporal analysis report. During days 1–21, 86% of major hemorrhages from DAPT (ASA + Clo) occurred compared to 25% of major hemorrhages from ASA alone [18]. In contrast, during days 22–90, only 14% of major hemorrhages from “DAPT” (Clo only) occurred compared to 75% from ASA alone [18].

Summary and Conclusions

Findings from the 2 recent trials initially seem to indicate an advantage for DAPT over ASA in preventing recurrent cerebral ischemic events, albeit limited to the first 7–10 days of treatment. However, the perceived advantages of DAPT may be partially reduced or entirely negated when considering the impact of minor (or any) hemorrhages as part of an overall outcome measure. Minor hemorrhages, which may be clinically relevant and require discontinuation of DAPT, may not have been adequately accounted for in the analyses presented in the available literature. In POINT, despite most hemorrhages being minor, and despite most minor hemorrhages occurring in the first several days of DAPT treatment, none of the analyses incorporated minor or any hemorrhage into a larger composite outcome. Similarly, in the com-

bined analyses for both CHANCE and POINT, minor hemorrhage was not included in any of the principal analyses, but was instead included only in an ancillary sensitivity analyses for which no numerical data or statistical details were provided by the investigators. Sensitivity analyses ascribing low relative clinical value may underestimate the clinical importance of nonmajor hemorrhages, and thereby overestimate the net benefit of DAPT over ASA.

It is likewise relevant that the 2 recent publications did not present data for the specific combined outcome of cerebral infarction plus any (major and minor) hemorrhage. A lack of information on such important endpoints specifically pertaining to the cerebrovascular patient may limit a comprehensive interpretation of the data, and an informed application of therapies.

In addition, data from CHANCE regarding major and minor hemorrhages may provide inaccurate information by including data from the period when Clo alone, and not ASA + Clo, was being compared to ASA alone, during which time substantially fewer major hemorrhages occurred in the “DAPT” group than in the ASA group. Inclusion of such data into a composite outcome of ischemic events plus hemorrhages may dilute the increased risk of hemorrhagic outcomes from DAPT, and incorrectly present a more favorable risk profile for DAPT relative to ASA alone. Secondary prevention trials have similarly identified a gradient in risk for major hemorrhages among various antiplatelet treatments, with DAPT having the greatest risk, ASA alone an intermediate risk, and Clo alone the lowest risk [21]. Including such confounding data may also impact long-term functional outcome measures, whereby the occurrence of fewer major hemorrhages from “DAPT” during Clo monotherapy introduces data from a period of relative protection against major hemorrhage, and potentially translates into factitiously lower disability rates for DAPT relative to the comparator ASA group.

Similar acute combination antiplatelet trials have revealed equivocal or negative results. The Fast Assessment of Stroke and TIA to prevent Early Recurrence (FASTER) trial randomized patients with TIA or minor infarct within 24 h to ASA plus Clo (300 mg once then 75 mg daily) or to ASA alone [11]. Due to low enrollment the trial was terminated prematurely and comprised 392 patients. At 90 days, DAPT was associated with numerically fewer primary cerebrovascular and secondary composite vascular outcome events, numerically more major hemorrhages (intracranial, moderate,

or severe), and a statistically greater rate of any symptomatic hemorrhage (3 vs. 0%, $p = 0.03$). The COMBination of Clo and ASA for Prevention of REcurrence in acute atherothrombotic Stroke Study (COMPRESS) randomized 334 patients with acute cerebral infarction due to intracranial or extracranial large vessel atherosclerotic stenosis within 48 h to ASA plus Clo (75 mg daily) or to ASA alone [9]. At 30 days, no differences were observed between the groups for the ischemic cerebrovascular (clinical or MRI-based) outcome measures, for the secondary composite vascular outcome, for severe hemorrhages (life endangering or major), or for the occurrence of any hemorrhage. Notable from these 2 investigations are the markedly discordant differences in serious (major or moderate/severe) hemorrhage rates for FASTER (2.5%) and COMPRESS (4%) in comparison to those of CHANCE (0.3%) and POINT (0.9%), which raise into question the generalizability and accuracy of the CHANCE and POINT findings. A recent observational study of 4,461 patients not eligible for enrollment in CHANCE or POINT due to nonminor infarcts, but who also received treatment within 24 h of symptoms, failed to demonstrate superiority of DAPT over ASA alone for all cerebrovascular (ischemic and hemorrhagic) events, and for the composite vascular/mortality outcome measure [22].

The Triple Antiplatelets for Reducing Dependency after Ischemic Stroke (TARDIS) trial randomized 3,096 patients with cerebral infarct or TIA within 48 h to a combination of ASA, Clo and dipyridamole (DP), or to “guideline” therapy consisting of ASA + DP, or Clo alone [23]. At 90 days, no advantage was observed for triple antiplatelet therapy in the primary outcome of recurrent infarct or TIA, whereas triple therapy substantially increased severe (fatal and major; $p = 0.0063$) and intracerebral hemorrhages ($p = 0.04$). While not specifically a study of ASA + Clo versus ASA, subgroup analysis data provided in the online appendix for the ASA + DP group (differing from the triple therapy group only by the omission of Clo) revealed no statistical differences in the primary ischemic outcome measure (Fig. S1), yet substantially fewer major hemorrhages (Fig. S4) in comparison to triple therapy [23]. Rates of serious (fatal/major/moderate) hemorrhages in the “guideline” ASA + DP or Clo only group (>2%) were again notably discrepant to those of CHANCE and POINT, again questioning the veracity and generalizability of the CHANCE and POINT findings and conclusions.

One theoretical dynamic that may occur as a result of DAPT discontinuation due to hemorrhage is subsequent

increased risk of infarction. In POINT, considering that the majority of all hemorrhage types occurred in the first 7–10 days [13], that platelet inhibition typically lasts several days from the time of discontinuation [24], and that any definitive advantage to DAPT had dissipated by the second study week [13], such a secondary consequence seems possible. However, no data exists comparing outcomes among patients in whom DAPT was discontinued versus those in whom DAPT was maintained, and partial or complete discontinuation of DAPT (one or both agents) is likely unavoidable once any symptomatic hemorrhage has occurred [17]. This point reinforces the importance of considering minor hemorrhages as outcome measures, since treatment strategies may change, and secondary adverse events may potentially ensue.

In summary, many questions and uncertainties exist regarding interpretation of the data from the 2 recent DAPT trials that raise valid concerns about the overall efficacy of early short-term DAPT following minor cerebral ischemic events. Currently, national guidelines in the US and the UK disagree on whether to recommend DAPT following minor infarction or TIA [25, 26].

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Statement of Ethics

This work complies with internationally accepted standards.

Disclosure Statement

The authors have no competing or conflicts of interest to declare.

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Author Contributions

Dr. Michael Moussouttas drafted the manuscript, and Dr. Nikolaos I.H. Papamitsakis reviewed the manuscript and provided comments and revisions. Both authors have approved of the final version of the manuscript for submission.

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