Antiplatelet Agents for Preventing Vaso-occlusive Events in People With Sickle Cell Disease: A Systematic Review

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Abstract: ***Background:*** Sickle cell disease (SCD) is the most common hemoglobinopathy, occurring worldwide, and vaso-occlusive events (VOEs) are its paramount, hallmark clinical manifestation. Evidence exists that platelets play an important role in generating VOEs. ***Objective:*** To assess the clinical benefits and harms of antiplatelet agents for preventing VOEs in patients with SCD. ***Methods:*** We conducted searches of the Cochrane Central Register of Controlled Trials (CENTRAL; up to 2018, issue 3 of 12), PubMed/MEDLINE (up to April 20, 2018), and the Excerpta Medica database (EMBASE; from 1980 to week 16 of 2018). We also searched the Latin American and Caribbean Health Sciences Literature (LILACS) database, the US Food and Drug Administration (FDA) website, the European Medicines Agency (EMA) website, the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP), and www.ClinicalTrials.gov. We checked the bibliographies of included studies and any relevant systematic reviews. Our systematic review included randomized clinical trials (RCTs) conducted in people who had SCD without VOEs at trial entry. Eligible trials compared a single or combination treatment regimen (with each treatment classified as a conventional or nonconventional antiplatelet agent) with conventional care, placebo, or another regimen. No restrictions were placed on the route of administration, dose, frequency, or duration of treatment. We selected RCTs, assessed the risk for bias, and extracted data in a duplicate and independent fashion. We estimated risk ratios for dichotomous outcomes and mean differences for continuous outcomes. We also subjected our analyses to a random-effects model, and Trial Sequential Analysis (TSA) was used. We used the grading of recommendations, assessment, development, and evaluation (GRADE) approach to assess the overall quality of data for each individual outcome. ***Results:*** We identified 5 RCTs (N=747) that met our criteria. Of these, 4 trials were multicenter and multinational. The trials included patients of all ages and assessed prasugrel, ticagrelor, crizanlizumab, and aspirin vs either placebo or no intervention. The most frequent route of administration was oral. The trials were small and carried a high risk for bias, given that pharmaceutical companies sponsored 4

of them. None of the trials reported information on quality of life. No meta-analysis was performed owing to heterogeneity in the ages of the participants and in the interventions. No single trial showed evidence of certainty regarding all-cause mortality. One trial showed uncertainty in comparing prasugrel vs placebo for preventing VOEs in patients younger than 18 years (relative risk [RR], 0.92; 95% CI, 0.80 to 1.06; low quality of evidence). TSA for this outcome suggested that a new trial should be conducted. One trial found a difference in the size effect of uncomplicated VOEs, favoring high-dose crizanlizumab vs placebo (mean difference, –1.50; 95% CI, –2.61 to –0.39; very low quality of evidence). No difference in VOEs was found in studies that compared either ticagrelor in children or prasugrel in adults vs placebo. The overall incidence of harms in any intervention did not differ from that in the control. **Conclusions:** The current evidence does not support or reject the use of any antiplatelet agent for preventing VOEs in people with SCD. This conclusion was based on small RCTs that carried a high risk for bias. No conclusive evidence exists regarding relevant clinical outcomes because the evidence is limited and of very low quality.

Introduction

Sickle cell disease (SCD) is the most common hemoglobinopathy worldwide.[1,2] The sickle hemoglobin is abnormal owing to a point mutation in the β-globin gene that results in the substitution of glutamic acid by valine at position 6 of the β-globin polypeptide chain.[3] According to the World Health Organization (WHO), SCD is a major public health problem. An estimated 70% of patients with SCD live in Africa,[2] and it is common among people of sub-Saharan African, Indian, Middle Eastern, or Mediterranean ancestry.[4,5] SCD includes homozygous hemoglobin S (HbSS), hemoglobin S combined with hemoglobin C (HbSC), hemoglobin S associated with β-thalassemia (sickle β0-Thal and sickle β+-Thal), and other, less prevalent doubly heterozygous conditions that cause clinical disease.[4,5] Sickle cell trait is generally asymptomatic and is not part of this review.

SCD is associated with morbidity and early mortality globally.[6] The paramount and hallmark clinical manifestation of SCD is the occurrence of painful crises—that is, vaso-occlusive events (VOEs)[7] caused by microvascular obstruction.[8] VOEs may also include stroke,[9] acute chest syndrome,[10] priapism,[11] and acute splenic sequestration.[12] The pathogenesis of VOEs is very complex.[13] It is explained by severe vasculopathy[14] that leads to a poor tolerance of any increase in blood viscosity or reduction in microcirculatory oxygenation.[13] The vasculopathy in SCD implies endothelial damage[15] that has an inflammatory component[16] and a chronic hypercoagulable component.[17] SCD is considered a thromboinflammatory disease,[18] given that platelets are the bridge that links inflammation to coagulation in SCD.[19]

Platelets are blood cells that play a major role in blood clot formation, inflammation, and cross-talk between other blood cells and endothelium.[20] Evidence exists of an effect of platelet hyperactivity in SCD on endothelium.[21,22] Either alone or in combination with other blood cells, platelets play a role in the development of VOEs.[23-26] Given that platelets play a pivotal role as mediators of inflammatory response, the use of antiplatelet agents for preventing VOEs in people with SCD appears to be logical.

Antiplatelet agents can be classified as conventional or nonconventional. The conventional antiplatelet agents are thromboxane inhibitors; platelet $P2Y_{12}$ receptor inhibitors; agents that influence cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP), and adenosine metabolism; and glycoprotein IIb/IIIa (GPIIb/IIIa) antagonists.

The thromboxane inhibitors are aspirin, dazoxiben, sulotroban, and picotamide[27]; the platelet $P2Y_{12}$ receptor inhibitors are thienopyridines (eg, ticlopidine, clopidogrel, and prasugrel) and nonthienopyridines (ticagrelor [Brilinta, AstraZeneca], cangrelor [Kengreal, Chiesi USA], and elinogrel)[28-31]; the agents that influence cAMP, cGMP, and adenosine metabolism are dipyridamole and cilostazol[32]; and the GPIIb/IIIa antagonists are abciximab (Reopro, Lilly), eptifibatide, and tirofiban (Aggrastat, Medicure Pharma).[33,34] The nonconventional antiplatelet agents are those that modulate the inflammatory actions of platelets or otherwise modify the disease, such as crizanlizumab.[35]

The role of antiplatelet agents in preventing VOEs is important for several reasons. First, VOEs are the hallmark sign of SCD.[8,36] Second, VOEs reduce the quality of life of patients with this disease.[37,38] Third, VOEs generally lead to hospitalization,[39] have an unpredictable course, and can be fatal.[7,39] Fourth, the only drug proven to be effective for preventing VOEs is hydroxyurea, which is not available widely and carries a risk for adverse events.[6] Therefore, the clinical benefits and harms of antiplatelet agents for preventing VOEs in people with SCD must be assessed.

Methods

Types of Studies

The studies included in this review were parallel-design randomized controlled trials (RCTs).

Types of Participants

The study participants were people of all ages with SCD who did not have VOEs at trial entry. We included participants with a history of VOEs.

Types of Interventions

Eligible trials compared single or combination treatment regimens (each treatment was classified as a conventional or nonconventional antiplatelet agent) with conventional care, placebo, or another regimen for preventing VOEs in people with SCD. The compared interventions included conventional and nonconventional antiplatelet agents (see above). We had no restriction regarding route of administration, dose, frequency, or duration.

Types of Outcomes

The primary outcomes were the following:

1. All-cause mortality during the trial;
2. Any VOE (eg, pain, stroke, acute chest syndrome, priapism, mesenteric vaso-occlusion, and any other VOE reported by trial authors) occurring at any time during the trial;
3. Adverse events (primarily any hemorrhage). We followed the recommendations outlined by Lineberry and colleagues.[40]

The secondary outcomes were quality of life (according to any validated scale, such as the Pediatric Quality of Life Inventory [PedsQL], the Sickle Cell Disease Quality of Life Inventory [SCD QoL], or the 36-Item Short Form Health Survey [SF-36]); number of days of hospitalization; and number of days of consumption of any type of analgesic.

Collection and Review of Data

We followed the Cochrane Collaboration reviewed methods for collection and analysis of summary data.[41] The protocol for this review was registered in the International Prospective Register of Systematic Reviews, also known as PROSPERO (CRD42018103524).

No limitations were set regarding publication status, country, duration of follow-up, or language. The search terms included the following: sickle cell, hemoglobinopathies, antiplatelet agents, vaso-occlusive, and prevention. We conducted searches of the Cochrane Central Register of Controlled Trials (CENTRAL; up to 2018, issue 3 of 12), PubMed/MEDLINE (up to April 20, 2018), and the Excerpta Medica database (EMBASE; from 1980 to week 16 of 2018; see Supplemental Material No. 1, "Search Strategies," at www.hematologyandoncology.net). We also searched the Latin American and Caribbean Health Sciences Literature (LILACS) database, the US Food and Drug Administration (FDA) website, the European Medicines Agency (EMA) website, the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP), and www.ClinicalTrials.gov. We also checked the bibliographies of included studies and any relevant systematic reviews (see Supplemental Material No. 1).

All studies were examined independently by 2 reviewers according to the inclusion criteria. One of the review authors checked for discrepancies, which were resolved by consensus. One review author entered the data into Review Manager 5.3.[42] A second author independently checked the data. Using a predesigned data extraction form, 2 reviewers independently extracted the data from the trial publications. The relevant data extracted from the included trials were study details (dates when research was conducted, geographic location, participant inclusion criteria, funding sources, publication date); participant characteristics (age, sex); SCD genotype; intervention details (type, duration, route of administration); outcome details (type of outcome, outcome assessment method); and bias assessment details (data necessary to assess the risk for bias, as described below).

Risk for Bias Assessment

We assessed the following risk for bias domains for each trial: allocation sequence generation, allocation concealment blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, for-profit bias, other bias.[43-47]

Overall, we judged trials as having a low risk for bias if we determined that they had a low risk for bias in either allocation sequence generation or allocation concealment.[48,49] In all other cases, we judged the trials as being at high risk for bias.

Measures of Treatment Effect

For binary outcomes, such as any VOE, adverse events, and all-cause mortality, we calculated the relative risk (RR) with 95% CIs and Trial Sequential Analysis (TSA)–adjusted CI (see below).

For continuous outcomes, such as quality of life, number of days of hospitalization, number of days of consumption of any type of analgesic, and number of VOEs, we calculated the mean difference with 95% CIs.

The unit of analysis was the participant. We used an intention-to-treat analysis. Owing to the lack of a

meta-analysis and the small sample size of the trials, we were not able to conduct a sensitivity analysis as we had planned.[50]

Meta-analysis

Had we pooled the data for a meta-analysis, it would have been conducted as detailed in PROSPERO.[51] We were unable to conduct the meta-analysis, however (see below), which in turn prevented us from conducting a full TSA.[52] We did, however, conduct a TSA for 1 trial[29] because it was a phase 3 trial that reported dichotomized data. To minimize random errors, we calculated the required information size (ie, the number of participants needed in a meta-analysis to detect or reject a certain plausible intervention effect).[53] The planned diversity-adjusted required information size was going to be based on the event proportion in the control group, assumption of a plausible RR reduction of 10% or the RR reduction observed in the included trials with low risk for bias, a 5% risk for a type 1 error, a 20% risk for a type 2 error, and the empiric diversity of the meta-analysis.[53] We used software from the Copenhagen Trial Unit to conduct the TSA.[54,55] We used the grading of recommendations, assessment, development, and evaluation (GRADE) system to assess the quality of the body of evidence associated with the following outcomes: all-cause mortality, any VOE, adverse events (total adverse events and study treatment–related adverse events), and quality of life.[56] We used GRADEPro software (http://gdt.guidelinedevelopment.org/central_prod/_design/client/handbook/handbook.html) to construct summary of findings tables.

Threshold for Clinical Relevance

To estimate the threshold for clinical relevance, we used a Bayes factor,[57] which is a likelihood ratio that shows the relative strength of evidence for 2 theories.[58,59] A Bayes factor provides a continuous measure of evidence for an experimental hypothesis (H1) over a null hypothesis (H0). When the Bayes factor is 1, the evidence does not favor either model over the other. As the Bayes factor increases above 1 (toward infinity), the evidence favors H1 over H0. As the Bayes factor decreases below 1 (toward 0), the evidence favors H0 over H1.[58] We used a Dienes calculator to determine the Bayes factor.

Results

Our search strategies found 5 trials (15 references) involving 747 randomly assigned participants who met our inclusion criteria[29,60-63] (Figure 1) according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[64]

The included trials were conducted between 1981 and 2017. Of the 5 trials, 4 studies were conducted multinationally,[29 60,62] and the remaining study was conducted in Nigeria.[61] One trial was phase 3,[29] three were phase 2,[60,62,63] and one did not report the phase.[61] Two trials reported mainly pharmacokinetics[60] and physiologic outcomes.[61] One trial included only children,[60] one included children and adolescents,[29] two included only adults,[62,63] and one included adolescents and adults.[61]

Two trials assessed oral prasugrel,[29,63] one assessed ticagrelor,[60] one assessed aspirin,[61] and one assessed crizanlizumab.[62] Four trials used placebo as the comparator,[29,60,62,63] and one used proguanil and folic acid as the control.[61] The FDA has not authorized the use of these drugs in people with SCD (see Supplemental Material No. 2 at www.hematologyandoncology.net).

We excluded 5 studies because they were case reports,[65] controlled clinical trials,[66] or systematic reviews,[67] or because they had a crossover design.[68,69] We detected 1 ongoing trial, HESTIA-2 (A Study to Assess the Effect of Ticagrelor in Reducing the Number of Days With Pain in Patients With Sickle Cell Disease), which is a randomized, double-blind, double-dummy, parallel-group, placebo-controlled study assessing 2 doses of ticagrelor (10 or 45 mg) in 90 patients with SCD, whose ages range from 18 to 30 years.[70] Recruitment has been completed. The primary outcome is change in the proportion of days with pain due to SCD; secondary outcomes are the average of the daily worst pain and change in the proportion of days with analgesic use. This trial will report safety data, such as number of major bleeding events or clinically relevant non-major bleeding events.

We detected 11 multiple publications, which were associated with 3 included trials and 1 excluded trial: the DOVE trial (A Study of Prasugrel in Pediatric Participants With Sickle Cell Disease; N=3),[29] the SUSTAIN trial (Study to Assess Safety and Impact of SelG1 With or Without Hydroxyurea Therapy in Sickle Cell Disease Patients With Pain Crises; N=4),[62] a trial by Wun and colleagues (N=3),[63] and a trial by Chaplin and colleagues (N=1).[65] We were unable to find the full text of 1 reference.[71]

Risk for Bias in Included Studies

Of the 5 trials, 3 (60%) were rated as having a low risk for selection bias because of their use of an appropriate random sequence generation method.[29,60,62] None of the trials reported any information regarding allocation concealment, however, and thus were rated as having an unclear risk for selection bias from this perspective. Of the 5 trials, 2 (40%) showed a low risk for performance bias and detection bias,[29,60] 2 (40%) had a low risk for detection bias,[29,62] 3 (60%) had a low risk for attrition bias,[29,60,63] and 4 (80%) had a low risk for reporting bias because relevant clinical outcomes were reported.[29,60,62,63]

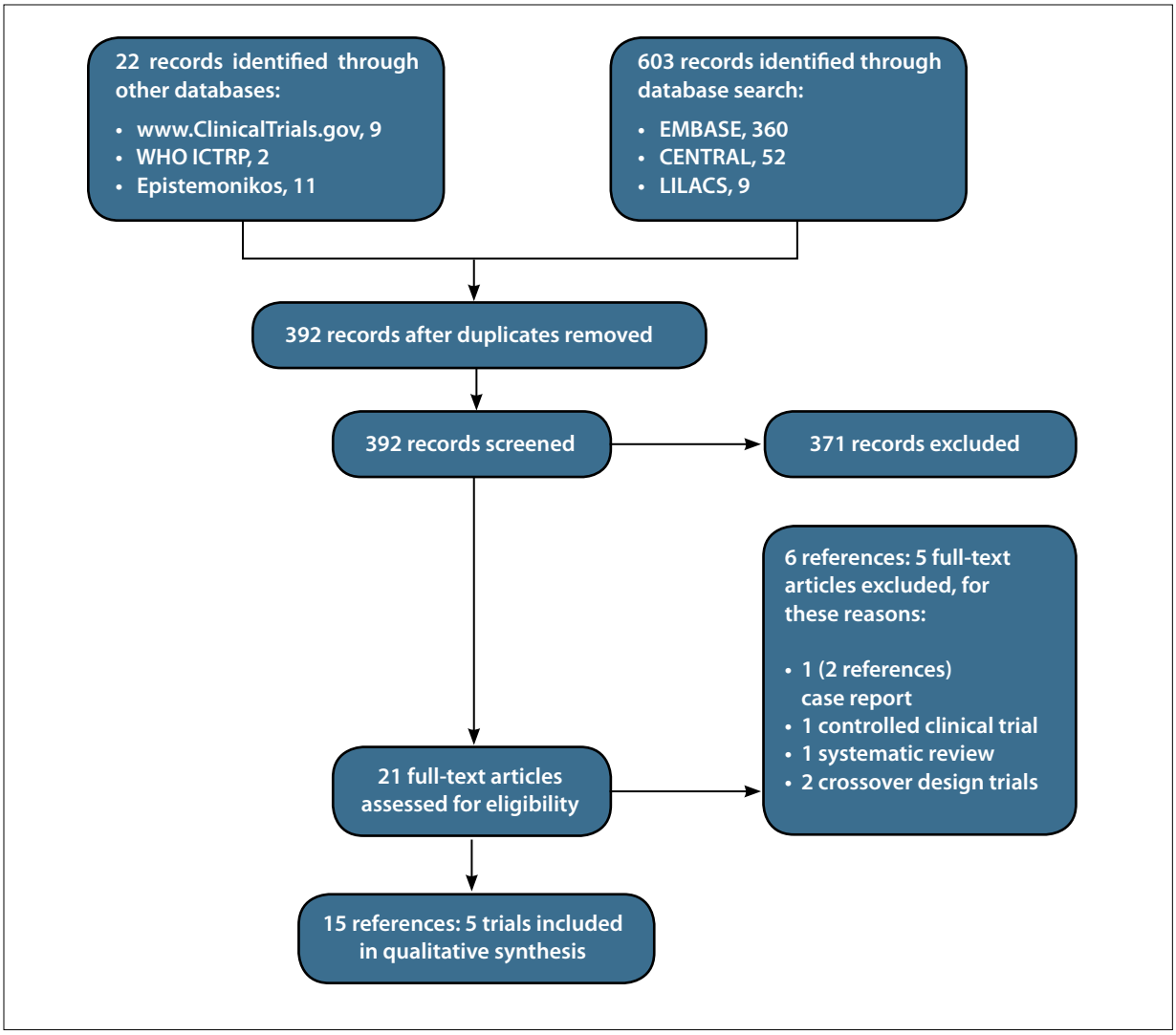

Figure 1. Algorithm describing the selection of studies for inclusion in the systematic review.

CENTRAL, Cochrane Central Register of Controlled Trials; EMBASE, Excerpta Medica database; LILACS, Latin American and Caribbean Health Sciences Literature; WHO ICTPR, World Health Organization International Clinical Trials Registry Platform.

Drug companies sponsored 4 trials.[29,60,62,63] Thus, they were rated as having a high risk for funding bias.

Effects of Interventions

Data on the effects of interventions are based on 4 RCTs that included 647 participants.[29,60,62,63] The trials reported no information about quality of life or number of days of consumption of any type of analgesic agents. One trial assessing aspirin plus proguanil and folic acid vs no intervention reported only physiologic endpoints.[61]

1. Primary Outcomes

(A) *All-Cause Mortality*

Prasugrel vs placebo: A study in children and adolescents[29] showed uncertainty regarding all-cause mortality with prasugrel vs placebo (1/170 [0.59%] vs 2/170 [1.2%]; RR, 0.50; 95% CI, 0.05 to 5.46; low quality of evidence owing to imprecision). The Bayes factor was 1.11. A TSA simulation with a proportion of 18% for all-cause mortality in the control group,[71] an RR reduction of 20%, an alpha of 5%, a beta of 20%, and diversity of 30% suggested an RCT including 3654 participants for assessing the size effect of prasugrel vs placebo on all-cause mortality in participants with SCD. Another trial[63] that included 62 adults reported no information on all-cause mortality.

Ticagrelor vs placebo: One trial with 25 children reported no difference in all-cause mortality with ticagrelor vs placebo.[60]

Crizanlizumab vs placebo: One trial[62] showed evidence of uncertainty regarding the rate of all-cause mortality with crizanlizumab vs placebo (3/130 [2.3%] vs 2/62 [3.2%]; RR, 0.72; 95% CI, 0.12 to 4.17; very low quality of evidence owing to imprecision). The Bayes factor was 1.01.

(B) *Uncomplicated Vaso-occlusive Events*

Prasugrel vs placebo: The DOVE trial[29] found no difference between prasugrel vs placebo in uncomplicated VOEs (113/171 [66.1%] vs 122/170 [71.8%]; RR, 0.92; 95% CI, 0.80 to 1.06; low quality of evidence owing to imprecision). The Bayes factor was 1.03. The TSA for uncomplicated VOEs suggested that a new RCT be conducted (Figure 2).

In adults,[63] one trial of prasugrel vs placebo showed a very low quality of evidence owing to a risk for bias and imprecision (9/40 [22.5%] vs 7/19 [36.8%]; RR, 0.61; 95% CI, 0.27 to 1.39). The Bayes factor was 1.58. The TSA for this outcome suggested a new trial with 1279 adults according to the following alpha-spending boundaries: proportion in the control group of 36.9%, RR reduction of 20%, alpha of 5%, and beta of 20% (Figure not shown).

Ticagrelor vs placebo: The HESTIA-1 trial (A Pharmacokinetic and Pharmacodynamic Dose-ranging Phase II Study of Ticagrelor in Paediatric Patients With Sickle Cell Disease) showed uncertainty regarding the difference between ticagrelor and placebo in uncomplicated VOEs (mean difference, 0.40; 95% CI, –0.73 to 1.53; very low quality of evidence owing to imprecision).[60]

Crizanlizumab vs placebo The SUSTAIN trial[62] reported a difference between high-dose crizanlizumab and placebo in uncomplicated VOEs (mean difference, –1.50; 95% CI, –2.61 to –0.39; very low quality of evidence owing to execution or imprecision). The Bayes factor for uncomplicated VOEs was 1.07.

(C) *Adverse Events*

Prasugrel vs placebo: The DOVE trial[29] found no differences between prasugrel and placebo in serious hemorrhagic events (34/170 [19.4%] vs 33/170 [20%]; RR, 1.03; 95% CI, 0.67 to 1.58), serious nonhemorrhagic events (87/170 [51.17%] vs 96/170 [56.47%]; RR, 0.91; 95% CI, 0.74 to 1.10), and hemorrhagic events requiring medical intervention (11/170 [6.47%] vs 8/170 [4.7%]; RR, 1.38; 95% CI, 0.57 to 3.33). The quality of evidence was low owing to imprecision.

Regarding treatment-emergent hemorrhage, Wun and colleagues[63] reported evidence of uncertainty (8/41 [19.5%] vs 1/19 [5.3%]; RR, 3.71; 95% CI, 0.50 to 27.57). The quality of evidence was very low owing to a risk for bias and imprecision.

Ticagrelor vs placebo: Evidence existed of uncertainty regarding differences in serious adverse events (1/16 [25%] vs 1/7 [14.3%]; RR, 1.75; 95% CI, 0.24 to 12.97) and nonserious adverse events (12/16 [75%] vs 5/7 [71.42%]; RR, 1.05; 95% CI, 0.61 to 1.82) in patients taking ticagrelor vs those taking placebo.[60] The quality of evidence was very low owing to imprecision.

Crizanlizumab vs placebo: The SUSTAIN trial,[62] which included participants exposed to either crizanlizumab or placebo, showed uncertainty regarding the number of patients with at least one serious adverse event (38/130 [29.2%] vs 17/62 [27.4%]; RR, 1.07; 95% CI, 0.66 to 1.73) or the number of patients with at least one adverse event (113/130 [86.92%] vs 55/62 [88.7%]; RR, 0.98; 95% CI, 0.88 to 1.09). The quality of evidence was very low owing to imprecision.

2. Secondary Outcomes

(A) *Complicated Vaso-occlusive Events*

Prasugrel vs placebo: The DOVE trial,[29] which compared prasugrel with placebo, found evidence of uncertainty regarding differences in acute chest syndrome (15/171 [8.8%] vs 15/170 [8.8%]; RR, 0.99; 95% CI, 0.50 to 1.97; low quality of evidence owing to imprecision). Wun and colleagues[63] reported no information about this outcome.

Ticagrelor vs placebo: The HESTIA-1 trial,[60] in a comparison of ticagrelor with placebo, reported evidence of uncertainty for differences in complicated VOEs (mean difference, 0.10; 95% CI, –0.22 to 0.42; very low quality of evidence owing to imprecision).

Crizanlizumab vs placebo: The SUSTAIN trial[62] reported no acute chest syndrome events in either group.

(B) *Vaso-occlusive Event–Induced Hospitalization*

Prasugrel vs placebo: The DOVE trial[29] reported no difference between prasugrel and placebo in the size effect for hospitalization owing to VOEs (69/171 [40.4%] vs 76/170 [44.7%]; RR, 0.90; 95% CI, 0.70 to 1.161; very low quality of evidence owing to imprecision). Wun and colleagues[63] reported no information about this outcome.

Ticagrelor vs placebo: The HESTIA-1 trial reported no information about VOE-induced hospitalization.[60]

Crizanlizumab vs placebo: The SUSTAIN trial found no difference between high-dose crizanlizumab and placebo in the size effect for hospitalization owing to VOEs (mean difference, –1.75; 95% CI, –8.74 to 5.25; N=137; very low quality of evidence owing to imprecision).[62]

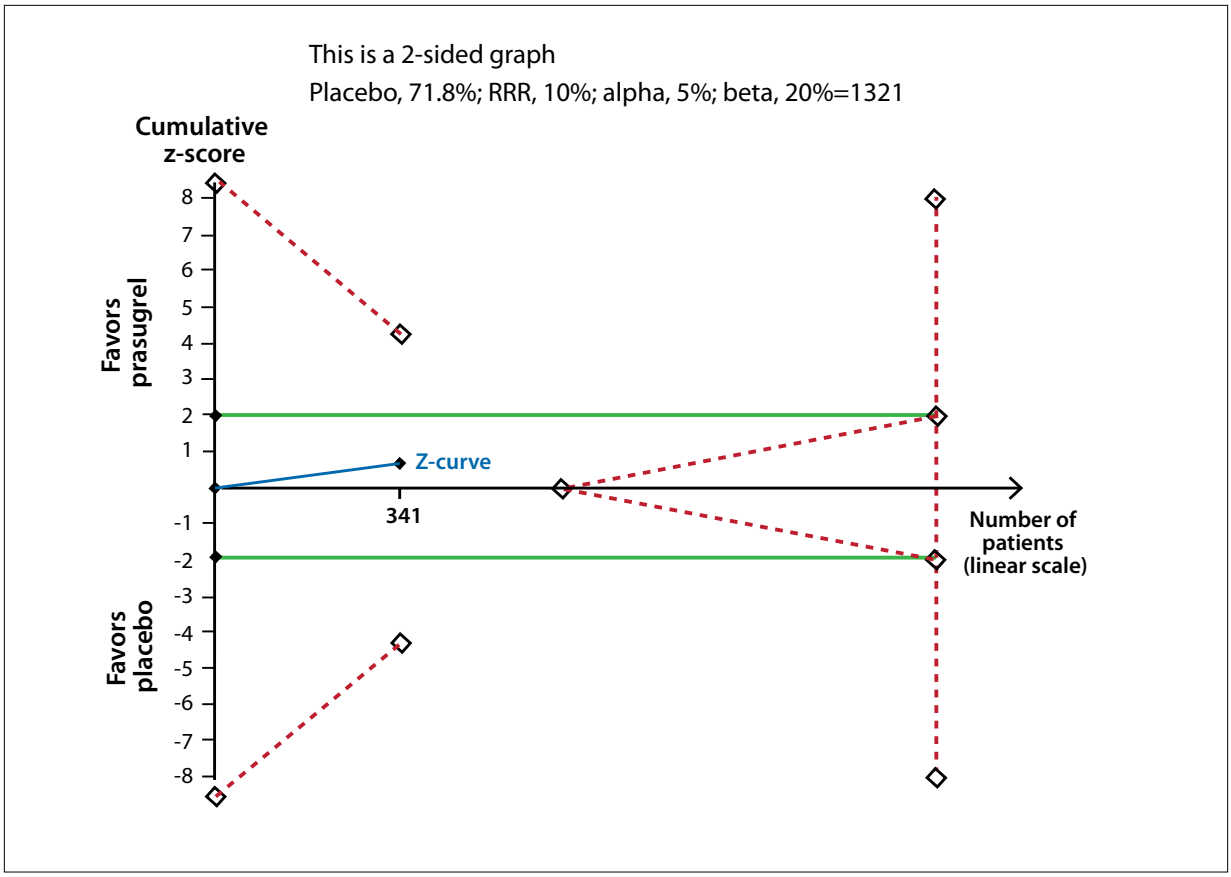

Figure 2. Trial Sequential Analysis (TSA)–adjusted CIs from a trial of prasugrel vs placebo for prevention of uncomplicated vaso-occlusive events (VOEs) in participants with sickle cell disease. VOEs were included if they occurred during either treatment or follow-up. Results were based on the diversity-adjusted required information size (DARIS) of 1321 patients. The calculation of this DARIS was based on the proportion of patients with an uncomplicated VOE, which was 71.8% in the control group. The relative risk reduction (RRR) was 10% in the experimental intervention group, with an alpha of 5% and a beta of 20%. The cumulative z-curve (blue line) did not cross the conventional alpha of 5% (green line) after 1 trial (ie, it did not reach statistical significance). The cumulative z-curve did not reach the futility area. The study population size is 341, which means that only 25.81% of the DARIS has been obtained.

DARIS, diversity-adjusted required information size; RRR, relative risk reduction; TSA, Trial Sequential Analysis; VOEs, vaso-occlusive events.

Data from Heeney MM et al. *N Engl J Med*. 2016;374(7):625-635;[29] analyzed using Trial Sequential Analysis software.[55]

Discussion

This systematic review of antiplatelet agents used to prevent VOEs in patients with SCD included 5 small RCTs (N=747). One trial included only adults; another trial included children, adolescents, and adults. These trials evaluated prasugrel,[29,63] ticagrelor,[60] aspirin,[61] and crizanlizumab,[62] comparing them with either placebo or no intervention. Crizanlizumab was administered intravenously. Overall, the trials were assessed as having a high risk for bias. Drug companies sponsored 4 of the 5 trials.[29,60,62,63] The trials were conducted between 1981 and 2017, and 4 of the 5 trials were multicenter and multinational.[29,60,62,63] One trial included none of the pre-specified outcomes of this systematic review.[61]

We were not able to conduct a meta-analysis for any intervention because of heterogeneity in the study populations, choice of study medication, and methods of assessing outcomes.

Trials assessing either prasugrel[29] or crizanlizumab[62] found no differences in all-cause mortality. Other trials reported either no deaths[60] or no information regarding mortality.[63] Only one trial reported a difference between crizanlizumab and placebo regarding uncomplicated VOEs.[62] With respect to serious or nonserious adverse events or complicated VOEs, all trials showed no

difference between study medications and control. In 2 trials that compared either prasugrel[29] or high-dose crizanlizumab[62] with placebo, no difference in the annual rate of days hospitalized was reported. No trial assessed, reported, or measured quality of life or number of days of consumption of any type of analgesic. The estimates of effect size were considered as very low owing to limitations in the trials related to either execution or imprecision (see Supplemental Material No. 3 at www.hematologyandoncology.net).

The analyses and conclusions are based on 4 multicenter and multinational small RCTs rated as having a high risk for bias owing to flaws in design or execution.[29,60,62,63] Thus, the overall completeness and applicability of the evidence could be considered low owing to potentially spurious findings. We identified heterogeneity in the sources of information, which consisted of a meeting abstract of a pharmacokinetic trial,[60] two phase 2 trials,[62,63] and one phase 3 trial.[29] These trials differed in objectives, follow-up periods, or sample sizes. All of these factors have a negative effect on the results, either quantitatively or qualitatively (see below). One trial[62] reported a difference between crizanlizumab and placebo in terms of uncomplicated VOEs, whereas another RCT reported neutral results (ie, no difference in effect size). Neutral effects should be considered not only "absence of evidence" but also "evidence of absence."[72] One trial[29] was stopped when an interim analysis suggested that clinical benefit outcomes were not being reached.[73,74] According to TSA, the prevention of VOEs in the DOVE trial[29] should be considered a false-negative result (Figure 2). Likewise, we cannot rule out that other results are false negatives,[29,60,63] nor can we rule out that the reduction in uncomplicated VOEs in the SUSTAIN trial[62] is a false positive, owing to the smallness of the sample size and the low number of events.

Drug companies sponsored 4 trials,[29,60,62,63] and the potential for bias related to drug company sponsorship has been described.[75] However, these RCTs reported information related to relevant clinical outcomes, including harms, across studies. Nonetheless, the smallness of the sample sizes and the low number of adverse events prevented reliable conclusions from being drawn.

For all outcomes, the quality of evidence was rated as low or very low, which leads to a very low degree of confidence in the estimates of effect. The true effects of these interventions on all outcomes are likely to be substantially different. This finding is explained by the high risk for bias found in all trials across several bias domains (eg, uncertainty in randomness, unclear risk of performance and detection biases, and attrition bias). In addition, we downgraded the quality of evidence for all reported outcomes on the basis of the smallness of the sample sizes in all trials, which yields statistical imprecision and wide CIs. This imprecision may be the consequence of a low or very low number of events.[75] Furthermore, evidence exists suggesting that RCTs conducted with small sample sizes are prone to selection bias.[76,77] On the basis of an analysis of the quality of evidence, the results of the trials should be interpreted as overestimating effect or underestimating harm.[78]

Because no meta-analysis was conducted, no statistical method could be used to detect publication bias. We believe that this systematic review has a low risk for publication bias, however, for the following reasons: our cautious search strategies (see Supplemental Material No. 1), our use of recommendations to reduce the chance of bias in elective inclusion and reporting of outcomes and analyses in systematic reviews of randomized trials of health care interventions,[44] and the fact that 4 of 5 RCTs had a low risk for selective outcome reporting bias, meaning that the chance of suppression of information was low.[79]

This systematic review has several limitations. First, as already discussed, it does not include a meta-analysis. As a result, the overall effect size and CI of any outcome or intervention are unknown. Furthermore, no subgroup analyses or sensitivity analyses were conducted. Second, the smallness of the sample sizes and the low or very low number of events in all the RCTs prevented TSA from being conducted for almost all outcomes. Third, the included RCTs lack methodologic strength. Nevertheless, this systematic review demonstrates the usefulness of evidence synthesis to find the therapeutic evidence available and appraise it critically. Finally, we were not able to obtain the full text of 1 study.[71] We hope to obtain this for a future update of our systematic review.

It has been suggested that the treatment effects shown in single-center RCTs are larger than those shown in multicenter RCTs.[80,81] Of 5 RCTs, 4 were multicenter and multinational, which represents a valuable finding of this review. This systematic review reported GRADE tables, which are an important tool for interpreting results and drawing conclusions.[82] Whenever possible, we conducted TSA to assess the potential need for further trials.[54]

Recently, Sins and colleagues[68] published an elegant systematic review of pharmacotherapeutic strategies in the prevention of acute, painful VOEs in SCD. Like us, they reported in the absence of meta-analysis. These 2 systematic reviews differ in many items. First, Sin and colleagues evaluated any pharmacologic strategies, whereas our review focused only on antiplatelet agents. Second, Sins and colleagues reported on 2 antiplatelet agents—the thromboxane inhibitor aspirin[27] and the platelet $P2Y_{12}$ receptor inhibitor ticlopidine[28]—in a section titled "Anticoagulation." Third, unlike Sins and colleagues, we excluded crossover design trials.[66-70] We concluded that

these exclusions did not affect the results of our review. Both trials[66-70] lack an appropriate description of the washout period and have other methodologic flaws.

Conclusions

This systematic review found no clear difference between antiplatelet agents and either placebo or no intervention in preventing VOEs in patients with SCD. All the evidence was rated as being of either low or very low quality owing to flaws in design and execution, small sample sizes, and a very low number of events. A paucity of reporting was available regarding all-cause mortality, complicated VOEs, hospitalization due to VOEs, and number of days of consumption of any type of analgesic. No information exists regarding quality of life. The harms profile of the antiplatelet agents in patients with SCD remains unknown. Results from an ongoing RCT that is assessing ticagrelor vs placebo will provide new information regarding these questions. In the interim, physicians and health policymakers should be cautious about the use of antiplatelet agents for preventing VOEs in patients with SCD.

There remains a need for powered RCTs to assess the benefits and harms of antiplatelet agents for preventing VOEs in people with SCD. Such trials should be designed according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)[83] and reported according to the Consolidated Standards of Reporting Trials (CONSORT) to improve the quality of reporting on efficacy.[84] The trials should follow recommendations regarding the reporting of adverse events.[40] Future trials should be planned according to the Patient-Centered Outcomes Research Institute (PCORI) recommendations.[85] New trials should include all-cause mortality, uncomplicated and complicated VOEs, and adverse events.

Disclosures

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Supplemental Material No. 1
Search Strategies

PubMed/MEDLINE up to April 20, 2018		
#1	"Anemia, Sickle Cell"[MeSH]	20447
#2	sickle cell[tiab]	22016
#3	#1 or #2	25809
#4	"Thienopyridines"[MeSH]	9771
#5	"Aspirin"[MeSH]	42208
#6	"Dipyridamole"[MeSH]	7531
#7	"Platelet Aggregation Inhibitors"[MeSH]	32494
#8	"Prasugrel Hydrochloride"[MeSH]	1090
#9	antiplatelet*[tiab]	23382
#10	thromboxane inhibitor*[tiab]	55
#11	P2Y12 receptor inhibitor*[tiab]	184
#12	aspirin[tiab]	44565
#13	dazoxiben[tiab]	0
#14	sulotroban[tiab]	53
#15	picotamide[tiab]	102
#16	thienopyridine*[tiab]	1327
#17	ticlopidine[tiab]	2454
#18	clopidogrel[tiab]	10986
#19	prasugrel[tiab]	1813
#20	ticagrelor[tiab]	1766
#21	cangrelor[tiab]	358
#22	elinogrel[tiab]	51
#23	dipyridamole[tiab]	7746
#24	cilostazol[tiab]	1537
#25	abciximab[tiab]	2010
#26	eptifibatide[tiab]	875
#27	tirofiban[tiab]	1103
#28	crizanlizumab[tiab]	6
#29	selg1[tiab]	0
#30	#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29	104899
#31	#3 and #30	182
EMBASE 1980 to week 16 of 2018		
1	exp sickle cell anemia/	(31945)
2	sickle cell.ti,ab.	(27985)
3	1 or 2	(35186)
4	exp thienopyridine derivative/	(2735)
5	exp acetylsalicylic acid/	(185694)
6	exp dipyridamole/	(21393)
7	exp antithrombocytic agent/	(306139)
8	exp prasugrel/	(6886)
9	antiplatelet*.ti,ab.	(37152)
10	thromboxane inhibitor*.ti,ab.	(68)
11	(aspirin or dazoxiben or sulotroban or picotamide or thienopyridine* or ticlopidine or clopidogrel or prasugrel or ticagrelor or cangrelor or elinogrel or dipyridamole or cilostazol or abciximab or eptifibatide or tirofiban or crizanlizumab or selg1).ti,ab.	(89053)
12	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	(323765)
13	3 and 12	(865)
14	random:.tw. or clinical trial:.mp. or exp health care quality/	(4513561)
15	13 and 14	(360)
CENTRAL up to 2018, issue 3 of 12		
#1	MeSH descriptor: [Anemia, Sickle Cell] explode all trees	478
#2	(sickle next cell):ti,ab	1300
#3	MeSH descriptor: [Thienopyridines] explode all trees	1621
#4	MeSH descriptor: [Aspirin] explode all trees	5055
#5	MeSH descriptor: [Dipyridamole] explode all trees	604
#6	MeSH descriptor: [Platelet Aggregation Inhibitors] explode all trees	3852
#7	MeSH descriptor: [Prasugrel Hydrochloride] explode all trees	228
#8	antiplatelet*:ti,ab	3627
#9	(thromboxane next inhibitor*):ti,ab	5
#10	(P2Y12 next receptor next inhibitor*):ti,ab	30
#11	aspirin:ti,ab	8603
#12	dazoxiben:ti,ab	0
#13	sulotroban:ti,ab	5
#14	picotamide:ti,ab	42
#15	thienopyridine:ti,ab	235
#16	ticlopidine:ti,ab	522
#17	clopidogrel:ti,ab	2808
#18	prasugrel:ti,ab	569
#19	ticagrelor:ti,ab	640
#20	cangrelor:ti,ab	70

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(Table continued from previous page)

#21	elinogrel:ti,ab	6
#22	dipyridamole:ti,ab	1011
#23	cilostazol:ti,ab	518
#24	abciximab:ti,ab	642
#25	eptifibatide:ti,ab	280
#26	tirofiban:ti,ab	385
#27	crizanlizumab:ti,ab	10
#28	selg1:ti,ab	3
#29	#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28	15874
#30	#1 or #2	1314
#31	#29 and #30	52

CENTRAL, Cochrane Central Register of Controlled Trials; EMBASE, Excerpta Medical database; exp, explosion of search term; MeSH, medical subject heating; tiab, title or abstract; ti,ab, title or abstract.

* and / refer to a wildcard; mp, multipurpose; tw, textword.

Supplemental Material No. 2
Characteristics of 5 Included Trials

Reference	Methods	Participants
DOVE trial Heeney et al, 2016 (PMID: 26644172)	- Parallel design - Two arms - Phase 3 - Thirteen countries in the Americas, Europe, Asia, and Africa; 51 sites - Follow-up period, median: 303 days in prasugrel group and 306 days in placebo group - Treatment duration: 9-24 months - Randomization unit: participant - Analysis unit: participant	- Type of sickle cell disease: HbSS - Enrolled: 341 - Randomized: prasugrel, 171; placebo, 170 - Age: children and adolescents, 2-17 years; mean (SD): prasugrel, 10.6 years (4.3); placebo, 10.6 years (4.3) - Gender, male: prasugrel, 49.4% (84/171); placebo, 49.1% (84/170) - Hydroxyurea use, No. (%): prasugrel, 77 (45.0); placebo, 76 (44.7) - VOCs in previous year, No. (SD): prasugrel: 3.5 (2.0); placebo, 4.0 (7.9) ***Inclusion criteria:*** 1. Children and adolescents (2-17 years of age); 2. Sickle cell anemia (HbSS or HbS/β0-Thal); 3. Two or more VOCs during previous year. ***Exclusion criteria:*** 1. Abnormal or conditional result of TCD within preceding year; 2. Current or past regular red cell transfusions for stroke prevention; 3. History of TIA, stroke, or head trauma; 4. Regular treatment with an antiplatelet agent, anticoagulant, or nonsteroidal anti-inflammatory drug; 5. Clinical findings associated with an increased risk for bleeding. The percentages of participants who adhered to the assigned regimen were similar in the 2 study groups (78.2% of participants in the prasugrel group and 81.2% of participants in the placebo group; *P*=.59). Diary data from 268 patients 4 years of age or older were collected for up to 9 months.
HESTIA-1 trial Hsu, ASH 2017	- Parallel design - Two arms: Part A, open-label dosing; Part B, study drug vs placebo - Countries: 6-10 in North America, Europe, Middle East, and Africa; approximately 30-37 sites with a minimum of 36 patients and a maximum of 50 patients (data gathered from study protocol) - Follow-up period: not stated - Treatment duration: 4 weeks - Randomization unit: participant - Analysis unit: participant	- Type of sickle cell disease: HbSS or HbS/β0-Thal - Randomization (Part B): started ticagrelor (0.75 mg/kg), 17; placebo, 8; completed ticagrelor (0.75 mg/kg), 14; placebo, 7 - Age, mean, 46 children with SCD: Part A: 11.2 years (range, 3-17); Part B: 10.0 years (range, 3-17); no discrimination by group - Gender, male: ticagrelor (0.75 mg/kg), 43.8% (7/16); placebo, 71.4% (5/7) - In part B, no difference was seen between pain ratings and analgesic use in the placebo and ticagrelor groups. The study was not statistically powered to detect differences in these outcomes. - Ticagrelor was well tolerated, with no bleeding during treatment. No patient discontinued treatment owing to an adverse event. ***Inclusion criteria:*** 1. Children aged ≥2 years and weighing up to 16 kg with a diagnosis of HbSS or HbS/β0-Thal; 2. If ≤16 years, must have had TCD within year preceding visit 1. If not, a TCD examination had to be done before entry in the study; 3. If ≥6 years, must have had an ophthalmologic examination within year preceding visit 1. If not, the patient had to be examined by an ophthalmologist before entry in the study; 4. If treated with an anti-sickling agent, such as hydroxyurea, weight-adjusted dose had to be stable for 1 month before enrollment; 5. Suitable venous access was required for study-related blood sampling. ***Exclusion criteria:*** 1. Previous history of TIA or clinically overt CVA (ischemic or hemorrhagic); 2. Severe head trauma, intracranial hemorrhage, intracranial neoplasm, arteriovenous malformation, aneurysm, or proliferative retinopathy; 3. Undergoing long-term red blood cell transfusion therapy; 4. Using NSAIDs for >3 days per week; 5. Undergoing long-term treatment with anticoagulants or antiplatelet drugs that cannot be discontinued. *For more inclusion and exclusion criteria, see https://www.clinicaltrialsregister.eu/ctr-search/trial/2014-001006-18/IT.*

	Interventions	Outcomes	Notes
	1. Oral prasugrel: Treatment was initiated at a dose of 0.08 mg/kg of body weight, with use of an individualized dose-adjustment strategy. Treatment was then adjusted to a dose between 0.04 and 0.12 mg/kg (maximum absolute dose, 10 mg). 2. Placebo 3. Co-intervention: hydroxyurea	- Primary: rate of VOCs (composite of painful crisis and acute chest syndrome) - Secondary: rate of sickle cell–related pain and intensity of pain (assessed daily with use of pain diaries); rate of hospitalizations for occlusive crisis, painful crisis, and acute chest syndrome; rate of sickle cell–related red cell transfusion; diary-documented rate of analgesic use and school attendance - Safety: incidence of hemorrhagic events requiring medical intervention; incidence of hemorrhagic and nonhemorrhagic adverse events that occurred while the participant was taking the study drug or placebo; rate of permanent discontinuation of the study drug or placebo owing to hemorrhagic and nonhemorrhagic adverse events	- Identifier: NCT01794000 - A priori sample size estimation: yes - Trial conduction date: May 2013-June 2015 - Sponsors: Daiichi Sankyo and Eli Lilly - Role of sponsor: not mentioned - One author affiliated with Daiichi Sankyo
	1. Ticagrelor: granules for oral suspension, 45 mg 2. Matching placebo for ticagrelor: granules for oral suspension ***Dose and treatment regimens:*** • Part A: 1. Open-label single doses (visits 2 and 3): initial dose of 0.75 mg/kg followed 7 days later by 1.125 or 2.25 mg/kg 2. Repeated dosing (visits 3 and 4): Patients self-administer open-label ticagrelor at 0.75 mg/kg twice daily within a 9- to 12-hour interval for 1 week. The first dose is administered in the evening after visit 3. Doses are adjusted following assessment by AstraZeneca and steering committee of the open-label Part A results in the first 6 to 12 patients. Dose adjustment decisions are based on a review of PK, PD, and adverse events. • Part B: Repeated dosing (visits 4-8): Randomization to twice-daily treatment with ticagrelor or placebo at visit 4. Patients self-administer placebo or ticagrelor at 0.75 mg/kg twice daily within a 9- to 12-hour interval for 4 weeks. The first dose is administered in the evening after visit 4. In both phases, doses are adjusted following assessment by AstraZeneca and steering committee of the open-label Part A results in the first 6 to 12 patients. Dose adjustment decisions are based on a review of PK, PD, and adverse events. Co-intervention: NSAIDs may not be administered more frequently than 3 days per week. Use of the ADP receptor blockers dipyridamole and cilostazol, oral or parenteral anticoagulants, and daily aspirin are not allowed in the study. Prophylactic doses of heparin are allowed.	- Primary: $P2Y_{12}$ reaction units, C_{max}, and AUC - Secondary: 1. Concentrations of ticagrelor and its active metabolite; population PK parameters (CL/F and AUC); 2. Investigation of efficacy of ticagrelor vs placebo in pediatric patients with SCD in reducing: • clinical symptoms • VOC • pain • other efficacy variables • days of analgesic use (ages ≥4 years only) • days of absence from school or work (ages ≥6 years only), excluding days of absence owing to study visits. - Safety assessments: 1. Laboratory safety variables; 2. Patient-reported outcomes.	- Identifier: NCT02214121 - A priori sample size estimation: no - Trial conduction date: not reported - Sponsor: AstraZeneca - Role of sponsor: involved in random sequence generation - Disclosures: declared. All trial authors have a relationship with the sponsor. Three authors are AstraZeneca employees. - Report of HESTIA-1 and NCT02214121 from www.ClinicalTrials.gov and study protocol were used to gather data.

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Reference	Methods	Participants
Osamo, 1981 (PMID: 6794308)	- Parallel design - Country: Nigeria - Follow-up period: 6 weeks - Randomization unit: participant - Analysis unit: participant	- Type of sickle cell disease: HbSS - Number enrolled: 100 - Randomized: aspirin, 50; control, 50 - Ages: between 11 and 20 years; information not reported for comparison group - Gender: not reported - Inclusion criteria: sickle cell disease - Exclusion criteria: not reported
SUSTAIN trial Ataga, 2017 (PMID: 27959701)	- Parallel design (3 arms) - Phase 2 - Three countries: United States, Brazil, and Jamaica; 60 sites - Screening phase: 30 days - Follow-up period: 52 weeks - Treatment duration: 52 weeks - Randomization unit: participant - Analysis unit: participant	- Randomized: 198 patients; high-dose crizanlizumab, 67; low-dose crizanlizumab, 66; placebo, 65 - Completed trial: 65.15% (129/198); high-dose crizanlizumab, 64.17% (43/67); low-dose crizanlizumab, 68.18% (45/66); placebo, 63.07% (41/65) - Age, median, years (range): high-dose crizanlizumab, 29 (16-63); low-dose crizanlizumab, 29 (17-57); placebo, 26 (16-56) - Gender, male, No. (%): high-dose crizanlizumab, 32 (48); low-dose crizanlizumab, 30 (45); placebo, 27 (42) - HbSS genotype, No. (%): high-dose crizanlizumab, 47 (70); low-dose crizanlizumab, 47 (71); placebo, 47 (72) - Concomitant hydroxyurea use, No. (%): high-dose crizanlizumab, 42 (63); low-dose crizanlizumab, 41 (62); placebo, 40 (62) - Patients with 2 to 4 sickle cell–related pain crises during previous 12 months, No. (%): high-dose crizanlizumab, 42 (63); low-dose crizanlizumab, 41 (62); placebo, 41 (63) ***Inclusion criteria:*** 1. Patients with SCD (HbSS, HbSC, HbS/β-Thal, HbS/β+-Thal, or other genotypes); 2. Age of 16-65 years; 3. History of 2-10 sickle cell–related pain crises in 12 months before enrollment in the trial ***Exclusion criteria:*** undergoing long-term red cell transfusion therapy
Wun, 2013 (PMID: 23414938)	- Parallel design - Phase 2 - Two countries: United States and Canada; 18 sites - Follow-up period: 60 days - Treatment duration: 30 days - Randomization unit: participant - Analysis unit: participant	- Type of participants: adults with SCD (genotypes: HbSS, HbSC, HbS/β0-Thal, and HbS-β+-Thal) - Randomized (62 patients): prasugrel, 41; placebo, 21 - Completed trial (57 patients): prasugrel, 39; placebo, 18 - Age, mean, years: prasugrel, 32.9; placebo, 31.5 - Gender, female: prasugrel: 21 (51.2%); placebo, 9 (42.9%) - Sickle cell genotype, No. (%): HbSC, 10 (25.0); 5 (23.8); HbSS, 24 (60.0); 13/21 (61.9) ***Inclusion criteria:*** 1. Adults aged 18-55 years; 2. SCD (genotypes HbSS, HbSC, HbS/β0-Thal, and HbS/β+-Thal); 3. Without diagnosis of acute VOC within 30 days. ***Exclusion criteria:*** 1. Severe hepatic or renal dysfunction; 2. Hematocrit <18%; 3. At risk for complications of excessive bleeding, including platelet count <100,000/mm^3; 3. Prior history of bleeding disorders, hemorrhagic or ischemic stroke, retinal hemorrhage, TIA, or intracranial hemorrhage.

	Interventions	Outcomes	Notes
	1. Intervention: oral aspirin (1.2 g of soluble acetylsalicylic acid per day in divided doses) plus proguanil and folic acid Duration: 6 weeks 2. Control: proguanil and folic acid Duration: 6 weeks	- Physiologic outcomes: Hb concentration; O_2 saturation (%); pO_2 (mm Hg); 2,3-DPG (μmol/mL) after 6 weeks of treatment *Outcomes were not described explicitly as primary endpoints.*	- Identifier: not stated - A priori sample size estimation: not reported - Trial conduction date: not reported - Sponsor: not given - Role of sponsor: not mentioned
	1. Loading dosing: 2 doses of crizanlizumab or placebo 2 weeks apart 2. Maintenance dosing: 1 dose every 4 weeks until 50 weeks; low-dose crizanlizumab (2.5 mg/kg of body weight); high-dose crizanlizumab (5.0 mg/kg); placebo; administered intravenously 3. Administration route: intravenous 4. Administration time: over a period of 30 minutes 5. Total doses administered: 14 Co-intervention: hydroxyurea for participants taking it before trial	- Primary: 1. Annual rate of sickle cell–related pain crises with high-dose crizanlizumab vs placebo (total number of crises × 365) ÷ (end date – date of randomization + 1); 2. Acute episodes of pain having no medically determined cause other than a vaso-occlusive event (acute chest syndrome, hepatic sequestration, splenic sequestration, priapism) and resulting in a medical facility visit and treatment with oral or parenteral narcotic agents or with a parenteral NSAID. - Secondary: 1. Annual rate of days hospitalized; 2. Times to first and second crises; 3. Annual rates of uncomplicated crises (defined as crises other than acute chest syndrome, hepatic sequestration, splenic sequestration, or priapism); 4. Acute chest syndrome; 5. Brief Pain Inventory score (long form with 1-week recall) - Adverse events: 1. During screening phase; 2. Before and after administration of crizanlizumab or placebo during treatment phase; 3. During follow-up evaluation phase.	- Identifier: NCT01895361 - A priori sample size estimation: yes - Trial conduction date: August 2013-January 2015 - Sponsors: Selexys Pharmaceuticals; grant to Selexys Pharmaceuticals from National Heart, Lung, and Blood Institute of National Institutes of Health (award No. 5R44HL093893); Orphan Products Grant Program of Food and Drug Administration (award No. R01FD004805) - Role of sponsor: not mentioned
	1. Oral prasugrel at 5 mg/d(n=41) or placebo (n=21) for 30 days 2. Co-intervention: hydroxyurea	- Primary: safety (hemorrhagic events requiring medical intervention) - Secondary: all adverse events, efficacy (frequency and intensity of pain ascertained by self-administered pain diary, frequency of pain requiring medical attention, and physiologic outcomes)	- Identifier: NCT01167023 - A priori sample size estimation: yes - Trial conduction date: August 26, 2010, to June 13, 2011 - Sponsors: Daiichi Sankyo and Eli Lilly - Role of sponsors: not mentioned - All authors affiliated with sponsor

ADP, adenosine diphosphate; AUC, area under the plasma concentration-time curve; CL/F, oral clearance; C_{max}, maximum plasma concentration; CVA, cerebrovascular accident; DPG, diphosphoglycerate; HbS/β+-Thal, sickle beta plus thalassemia; HbS/β0-Thal, sickle beta zero thalassemia; HbSC, sickle hemoglobin C disease; HbSS, homozygous hemoglobin S; NSAIDs, nonsteroidal anti-inflammatory drugs; PD, pharmacodynamics; PK, pharmacokinetics; SCD, sickle cell disease; SD, standard deviation; TCD, transcranial Doppler; TIA, transient ischemic attack; VOC, vaso-occlusive crisis.

Supplemental Material No. 3
Summary of Findings Tables According to Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Approach

Question: Should prasugrel vs placebo be used in children and adolescents with sickle cell disease?[1]

Heeney MM, Hoppe CC, Abboud MR, et al; DOVE Investigators. A multinational trial of prasugrel for sickle cell vaso-occlusive event. *N Engl J Med.* 2016;374(7):625-635.

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects *Time frame: May 2013-June 2015*[2]	
Participants (Studies), Follow-up	Risk for Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With Placebo	With Prasugrel	Relative Effect (95% CI)	Risk With Placebo	Risk Difference With Prasugrel (95% CI)
Mortality from any cause during any time of trial (critical outcome)											
340 (1 study), 303 in prasugrel group and 306 in placebo group)[5]	No serious risk for bias	No serious inconsistency	No serious indirectness	Very serious[3]	Undetected	++-- Low[3] owing to imprecision	2/170 (1.2)[4]	1/170 (0.59)	RR 0.50 (0.05-5.46)	12 per 1000[4]	6 fewer per 1000 (from 11 fewer to 52 more)
Uncomplicated vaso-occlusive event during any time of trial, either treatment or follow-up phase (critical outcome)											
341 (1 study), 303 in prasugrel group and 306 in placebo group[5]	No serious risk for bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	++-- Low	122/170 (71.8)[6]	113/171 (66.1)	RR 0.92 (0.80-1.06); adjusted with Trial Sequential Analysis RR 0.92 (alpha-spending adjusted 95% CI, 0.53-1.59)	718 per 1000[6]	57 fewer per 1000 (from 144 fewer to 43 more)
Adverse events, mainly any hemorrhage (critical outcome)											
340 (1 study), 303 in prasugrel group and 306 in placebo group[5]	No serious risk for bias	No serious inconsistency	No serious indirectness	Serious[7]	Undetected	+++- Moderate owing to imprecision	33/170 (19.4)[8]	34/170 (20)	RR 1.03 (0.67-1.58)	194 per 1000[8]	6 more per 1000 (from 64 fewer to 113 more)
Acute chest syndrome: complicated vaso-occlusive event (stroke, acute chest syndrome, priapism) during any time of trial, either treatment or follow-up phase (critical outcome)											
341 (1 study), 303 in prasugrel group and 306 in placebo group[5]	No serious risk for bias	No serious inconsistency	No serious indirectness	Serious[9]	Undetected	++-- Low[9] owing to imprecision	15/170 (8.8)[10]	15/171 (8.8)	RR 0.99 (0.50-1.97)	88 per 1000[10]	1 fewer per 1000 (from 44 fewer to 86 more)

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Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects *Time frame: May 2013-June 2015*[2]	
Participants (Studies), Follow-up	**Risk for Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Overall Quality of Evidence**	**With Placebo**	**With Prasugrel**	**Relative Effect (95% CI)**	**Risk With Placebo**	**Risk Difference With Prasugrel (95% CI)**
Quality of life: not reported											
-	-	-	-	-	-	See comment.	-	0	-	See comment.	This outcome was not reported in DOVE trial.

RR, relative risk.

[1] Type of sickle cell disease: homozygous hemoglobin S (HbSS).

[2] Fifty-one centers in the Americas, Europe, Asia, and Africa. Trial was sponsored by Daiichi Sankyo and Eli Lilly.

[3] Downgraded 2 levels for imprecision (very low number of events and small sample size with an impact on the precision of the effect estimates).

[4] Data obtained from number of deaths in placebo group.

[5] Treatment duration: 9-24 months.

[6] Data obtained from number of painful crises in placebo group.

[7] Downgraded 1 level for imprecision (low number of events).

[8] Data obtained from hemorrhagic adverse events in placebo group.

[9] Downgraded 2 levels for imprecision (low number of events).

[10] Data obtained from number of cases of acute chest syndrome in placebo group.

Question: Should ticaglerol vs placebo be used in children and adolescents with sickle cell disease?[1]

Hsu LL, Sarnaik S, Williams S, Amilon C, Wissmar J, Berggren A; HESTIA1 Investigators. A dose-ranging study of ticagrelor in children aged 3-17 years with sickle cell disease: a 2-part phase 2 study. *Am J Hematol.* 2018;93(12):1493-1500. doi:10.1002/ajh.25273.

Quality Assessment							**Summary of Findings**				
Participants (Studies), Follow-up	**Risk for Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Overall Quality of Evidence**	**Study Event Rates (%)**		**Relative Effect (95% CI)**	**Anticipated Absolute Effects**	
							With Placebo	**With Ticagrelor**		**Risk With Placebo**	**Risk Difference With Ticagrelor (95% CI)**
Mortality from any cause											
-	-	-	-	-	-	See comment.	-	-	-	0/7	0/16
Uncomplicated vaso-occlusive events during any time of trial, either treatment or follow-up phase (critical outcome; better outcome indicated by lower values)											
23 (1 study[2]), 4 weeks[5]	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[4]	Undetected	+--- Very low[3,4] owing to risk for bias, imprecision	8	15	MD 0.40 higher (0.73 lower to 1.53 higher)	The mean number of uncomplicated vaso-occlusive events during any time of the trial, either treatment or follow-up phase, in the control group was 0.6 times the number of vaso-occlusive crises.	The mean number of uncomplicated vaso-occlusive events during any time of the trial, either treatment or follow-up phase, in the intervention group was 1.
Adverse events (critical outcome)											
23 (1 study[2]), 4 weeks[5]	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[4]	Undetected	+--- Very low[3,4] owing to risk for bias, imprecision	1/7 (14.3)[6]	4/16 (25)	RR 1.75 (0.24-12.97)	143 per 1000[6]	107 more per 1000 (from 109 fewer to 1000 more)
Complicated vaso-occlusive event (stroke, acute chest syndrome, priapism) during any time of trial either treatment or follow-up phase: not reported											
-	-	-	-	-	-	See comment.	-	-	-	See comment.	HESTIA-1 trial did not report this outcome.

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Quality Assessment							Summary of Findings				
Participants (Studies), Follow-up	Risk for Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Study Event Rates (%)		Relative Effect (95% CI)	Anticipated Absolute Effects	
							With Placebo	With Ticagrelor		Risk With Placebo	Risk Difference With Ticagrelor (95% CI)
Quality of life: not reported											
-	-	-	-	-	-	See comment.	-	-	-	See comment.	HESTIA-1 trial did not report this outcome.

MD, mean difference; RR, relative risk.

[1] Homozygous hemoglobin S (HbSS) or sickle beta zero thalassemia (HbS/β0).

[2] Phase 2 sponsor was AstraZeneca.

[3] Downgraded 1 level owing to limitations in trial execution (high attrition bias): 11.42 % (4/35). This trial was designed to assess pharmacokinetics, pharmacodynamics, and safety of ticagrelor.

[4] Downgraded 2 levels owing to imprecision (very low sample and number of events with an impact in the precision of the effect estimates).

[5] Data regarding treatment duration.

[6] Assumed risk was estimated by using data from control group.

Question: Should crizanlizumab vs placebo be used in adolescents and adults with sickle cell disease?[1]

Ataga KI, Kutlar A, Kanter J, et al. Crizanlizumab for the prevention of pain crises in sickle cell disease. *N Engl J Med*. 2017;376(5):429-439.

Quality Assessment							**Summary of Findings**				
							Study Event Rates (%)			**Anticipated Absolute Effects** *Time frame: August 2013-January 2015*[2]	
Participants (Studies), Follow-up	**Risk for Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Overall Quality of Evidence**	**With Placebo**	**With Crizanlizumab**	**Relative Effect (95% CI)**	**Risk With Placebo**	**Risk Difference With Crizanlizumab (95% CI)**
Mortality from any cause during any time of trial (critical outcome)											
192 (1 study[3]), 52 weeks	Very serious[4]	No serious inconsistency	No serious indirectness	Serious[5]	Undetected	+--- Very low[4,5] owing to risk for bias, imprecision	2/62 (3.2)[6]	3/130 (2.3)	RR 0.72 (0.12-4.17)	32 per 1000[6]	9 fewer per 1000 (from 28 fewer to 102 more)
Uncomplicated vaso-occlusive event during any time of trial, either treatment or follow-up phase (critical outcome; better outcome indicated by lower values)											
132 (1 study[3]), 52 weeks	Very serious[4]	No serious inconsistency	No serious indirectness	Serious[5]	Undetected	+--- Very low[4,5] owing to risk for bias, imprecision	65[7]	67[8]	MD –1.50 (–2.61 to –0.39)	The mean number of uncomplicated vaso-occlusive events during any time of the trial, either treatment or follow-up phase, in the control group was 3.38 times the number of crises per year in the intervention group.	The mean number of uncomplicated vaso-occlusive events during any time of the trial, either treatment or follow-up phase, in the intervention group was 1.5 times lower (range, 2.61 to -0.39).
Adverse event (No. of patients with ≥1 serious adverse event; critical outcome)											
192 (1 study[3]), 52 weeks	Not serious	No serious inconsistency	No serious indirectness	Very serious imprecision	Undetected	+--- Very low[5] owing to imprecision	17/62 (27.4)[1]	38/130 (29.2)	RR 1.07 (0.66-1.73)	274 per 1000[9]	19 more per 1000 (from 93 fewer to 200 more)
Complicated vaso-occlusive event (stroke, acute chest syndrome, priapism) during any time of trial, either treatment or follow-up phase: not reported											
-	-	-	-	-	-	See comment.	-	-	-	See comment.	SUSTAIN trial reported no events.

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Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects *Time frame: August 2013-January 2015*[2]	
Participants (Studies), Follow-up	Risk for Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With Placebo	With Crizanlizumab	Relative Effect (95% CI)	Risk With Placebo	Risk Difference With Crizanlizumab (95% CI)
Quality of life: not reported											
-	-	-	-	-	-	See comment.	-	-	-	See comment.	SUSTAIN trial did not report this outcome.

MD, mean difference; RR, relative risk.

[1] Patients with sickle cell disease (homozygous hemoglobin S [HbSS], sickle hemoglobin C disease [HbSC], sickle beta zero thalassemia [HbS/β0-Thal], sickle beta plus thalassemia [HbS/β+-Thal], or other genotypes).

[2] Sixty centers in the United States, Brazil, and Jamaica. Sponsored by Daiichi Sankyo and Eli Lilly.

[3] Phase 2, parallel design trial.

[4] Downgraded 2 levels owing to high level of attrition. Early withdrawals, 34.84% (69/198); completed trial, 65.15% (129/198).

[5] Downgraded 2 levels owing to very low number of events and small sample size (with an impact on precision of the effect estimates).

[6] Assumed risk based on data from placebo group.

[7] Placebo.

[8] High doses of crizanlizumab (5.0 mg/kg).

[9] Assumed risk estimated from placebo group data.

Question: Should prasugrel vs placebo be used in adults with sickle cell disease?[1]

Wun T, Soulieres D, Frelinger AL, et al. A double-blind, randomized, multicenter phase 2 study of prasugrel versus placebo in adult patients with sickle cell disease. *J Hematol Oncol*. 2013;6:17.

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects *Time frame: August 26, 2010, to June 13, 2011*[2,3]	
Participants (Studies), Follow-up	Risk for Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With Placebo	With Prasugrel	Relative Effect (95% CI)	Risk With Placebo	Risk Difference With Prasugrel (95% CI)
Mortality from any cause during any time of trial: not reported											
-	-	-	-	-	-	See comment.	-	-	-	See comment.	Trial did not report this outcome.
Uncomplicated vaso-occlusive event during any time of trial, either treatment or follow-up phase (critical outcome)											
59 (1 study), 60 days[7]	Serious[4]	No serious inconsistency	No serious indirectness	Very serious[5]	Undetected	+--- Very low[4,5] owing to risk for bias, imprecision	7/19 (36.8)[6]	9/40 (22.5)	RR 0.61 (0.27-1.39)	368 per 1000[6]	144 fewer per 1000 (from 269 fewer to 144 more)

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Quality Assessment							Summary of Findings				
Participants (Studies), Follow-up	Risk for Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Study Event Rates (%)		Relative Effect (95% CI)	Anticipated Absolute Effects *Time frame: August 26, 2010, to June 13, 2011*[2,3]	
							With Placebo	With Prasugrel		Risk With Placebo	Risk Difference With Prasugrel (95% CI)
Adverse event, mainly any hemorrhage: treatment-emergent (critical outcome)											
60 (1 study), 60 days[7]	Serious[4]	No serious inconsistency	No serious indirectness	Very serious[5]	Undetected	+--- Very low[4,5] owing to risk for bias, imprecision	1/19 (5.3)[6]	8/41 (19.5)	RR 3.71 (0.50-27.57)	53 per 1000[6]	143 more per 1000 (from 26 fewer to 1000 more)
Acute chest syndrome: complicated vaso-occlusive event (stroke, acute chest syndrome, priapism) during any time of trial, either treatment or follow-up phase: not reported											
-	-	-	-	-	-	See comment.	-	-	-	See comment.	Trial did not report this outcome.
Quality of life: not reported											
-	-	-	-	-	-	See comment.	-	-	-	See comment.	Trial did not report this outcome.

RR, relative risk.

[1] Type of participants: adults with SCD (genotypes HbSS, HbSC, HbS/β0-Thal, and HbS/β+-Thal).

[2] Two centers in the United States and Canada.

[3] Sponsored by Daiichi Sankyo and Eli Lilly.

[4] Downgraded 1 level owing to lack of information about trial design and execution.

[5] Downgraded 2 levels owing to very low number of events and small sample size (with an impact on precision of the effect estimates).

[6] Assumed risk estimated from placebo group data.

[7] Treatment duration: 30 days.

GRADE Working Group Grades of Evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect (++++)

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate (+++-)

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate (++--)

Very low quality: We are very uncertain about the estimate (+---)