U.S. Food and Drug Administration
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Drug Safety Communications

**FDA Drug Safety Communication: FDA review finds long-term treatment with blood-thinning medicine Plavix (clopidogrel) does not change risk of death**

This is an update to the FDA Drug Safety Communication: FDA Reviews Long-Term Antiplatelet Therapy as Preliminary Trial Data Show Benefits but a Higher Risk of Non-Cardiovascular Death issued on November 16, 2014.

**Safety Announcement**

**[11-06-2015]** A U.S. Food and Drug Administration (FDA) review has determined that long-term use of the blood-thinning drug Plavix (clopidogrel) does not increase or decrease overall risk of death in patients with, or at risk for, heart disease. Our evaluation of the Dual Antiplatelet Therapy (DAPT)[1] trial and several other clinical trials also does not suggest that clopidogrel increases the risk of cancer or death from cancer.

Patients should not stop taking clopidogrel or other antiplatelet medicines because doing so may result in an increased risk of heart attacks and blood clots. Talk with your health care professional if you have any questions or concerns about clopidogrel. Health care professionals should consider the benefits and risks of available antiplatelet medicines before starting treatment.

Clopidogrel is an antiplatelet medicine used to prevent blood clots in patients who have had a heart attack, stroke, or problems with the circulation in the arms and legs. It works by helping to keep the platelets in the blood from sticking together and forming clots that can occur with certain medical conditions.

In order to investigate the increased risk of death and cancer-related death reported with clopidogrel in a large clinical trial called the Dual Antiplatelet Therapy (DAPT) trial, we examined the results of the DAPT trial and other large, long-term clinical trials of clopidogrel with data available on rates of death, death from cancer, or cancer reported as an adverse event.[2-13]

Results from the DAPT trial were published in the *New England Journal of Medicine* in November 2014. The DAPT trial compared treatment with dual antiplatelet therapy (either clopidogrel [Plavix] or prasugrel [Effient] plus aspirin) for 12 months versus 30 months in patients who had undergone placement of a drug-eluting coronary stent. Compared to patients taking clopidogrel for 12 months, patients who were treated with clopidogrel for 30 months had lower rates of heart attacks and stent thrombosis but higher rates of death, primarily from cancer or trauma.

We performed meta-analyses looking at the results from multiple other long-term clinical trials to assess the effects of clopidogrel on death rates from all causes. The results indicate that long-term (12 months or longer) dual antiplatelet therapy with clopidogrel and aspirin do not appear to change the overall risk of death when compared to short-term (6 months or less) clopidogrel and aspirin, or aspirin alone. Also, there was no apparent increase in the risks of cancer-related deaths or cancer-related adverse events with long-term treatment.

The following table shows the results from the meta-analyses:

| | **Number of patients included** | **Long-term clopidogrel plus aspirin** | **Short term clopidogrel plus aspirin or aspirin alone** |
|---|---|---|---|
| Overall incidence of death | 56,799 | 6.7% | 6.6% |
| Incidence of cancer adverse events | 37,835 | 4.2% | 4.0% |
| Incidence of cancer death | 40,855 | 0.9% | 1.1% |

We urge health care professionals and patients to report side effects involving clopidogrel or other antiplatelet medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

**Facts about Clopidogrel**

- Clopidogrel is an antiplatelet medicine used to reduce the risk of heart attacks, strokes, and other clot-related conditions in patients who have had a previous heart attack, stroke, or problems with the circulation in the arms and legs. It works by keeping the platelets in the blood from sticking together, thereby preventing blood clots that can occur with certain cardiovascular conditions.
- Clopidogrel is sold under the brand name Plavix and as generics.
- Clopidogrel increases the risk of bleeding.
- Taking clopidogrel with certain medicines may increase your risk of bleeding. Tell your health care professional if you take any of the following:
    - Aspirin, especially if you have had a stroke. Always ask your health care professional about whether you should take aspirin with clopidogrel to treat your condition.
    - Non-steroidal anti-inflammatory drugs (NSAIDS), such as ibuprofen and naproxen. Ask your health care professional for a list of NSAID medicines if you are not sure.
    - Warfarin (Coumadin, Jantoven).
    - Selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs).
- Other common side effects of clopidogrel can include shortness of breath.

**Additional Information for Patients and Caregivers**

- Based on our reviews of the Dual Antiplatelet Therapy (DAPT) trial and several other large clinical trials, we have concluded that treatment with clopidogrel for more than one

year does not appear to change the overall risk of death in patients with, or at risk for, coronary artery disease.

- Clopidogrel is an antiplatelet blood-thinning medicine that may help prevent future heart attacks, strokes, and other clot-related diseases in patients who have already had a heart attack, stroke, or have certain cardiovascular conditions.
- Do not stop taking clopidogrel without first talking to your health care professional. Suddenly stopping the use of antiplatelet medicines can put you at risk for heart attacks, strokes, and blood clots.
- Be aware that while taking clopidogrel you may bruise more easily, and it may take longer for any bleeding to stop.
- Discuss any questions or concerns about clopidogrel with your health care professional.
- Read the patient Medication Guide you get along with your clopidogrel prescriptions. It explains the benefits and risks associated with the use of clopidogrel.
- Report any side effects you experience to your health care professional and the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

**Additional Information for Health Care Professionals**

- Based on our reviews of the Dual Antiplatelet Therapy (DAPT) trial and several other large, long-term clinical trials, we have concluded that there is no evidence of either a harmful or beneficial effect of clopidogrel on all-cause mortality or cancer-related deaths in a population with, or at risk for, coronary artery disease. That is, the adverse mortality findings in the DAPT trial were not confirmed.
- We are working with the manufacturers of clopidogrel to update the label to reflect the results of the mortality meta-analysis.
- Clopidogrel is approved for use in combination with aspirin in patients with acute coronary syndrome, or in patients not on aspirin with a history of recent myocardial infarction, recent stroke, or established peripheral arterial disease. Clopidogrel is not indicated for secondary prevention of cardiovascular events (see Section 14.3 of the drug label).
- When selecting antiplatelet therapy for patients with an acute coronary syndrome who are managed with coronary stent implantation, prescribers should consider that prasugrel and ticagrelor have been shown to be superior to clopidogrel when used in this patient population. In addition, in patients with a history of myocardial infarction one to three years prior to study enrollment, ticagrelor has also been shown to reduce the risk of cardiovascular death, myocardial infarction, and stroke.
- Inform patients about the increased risk of bleeding and bruising when taking clopidogrel.
- Advise patients to report any unanticipated, prolonged, or excessive bleeding, or blood in their stools or urine.
- Encourage patients and caregivers to read the patient Medication Guide they received with clopidogrel prescriptions.
- Report adverse events involving clopidogrel to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

**Data Summary**

The Dual Antiplatelet Therapy (DAPT)[1] trial was a randomized, double-blind, placebo-controlled trial that compared antiplatelet treatment for 30 months vs. 12 months following percutaneous coronary intervention and placement of a drug-eluting stent. After stent placement, patients received 12 months of dual antiplatelet therapy consisting of aspirin plus either clopidogrel (Plavix) or prasugrel (Effient) and then were randomized to continued treatment for 18 additional months of dual antiplatelet therapy (aspirin plus clopidogrel or prasugrel) or to aspirin plus placebo. The investigators selected the antiplatelet agents patients received, with about two-thirds receiving clopidogrel and one-third receiving prasugrel. Acute coronary syndrome was the indication for the stent in about 46% of patients.

The DAPT trial showed that the 30-month extended antiplatelet therapy with clopidogrel or prasugrel decreased the risk of stent thrombosis and heart attacks, but increased the risk of bleeding and overall risk of death compared to the 12-month group. The higher rate of death was primarily due to a larger number of deaths from non-cardiovascular causes, principally cancer and trauma. The increased rate of death was evident in patients receiving clopidogrel but not prasugrel.

In order to investigate the signals of increased risk of death and cancer-related death from the DAPT trial, FDA evaluated the DAPT trial and performed trial-level meta-analyses of other large, long-term trials that had available data on rates of death, rates of death from cancer, or rates of cancer adverse events. Trials included in the meta-analyses had a clopidogrel plus aspirin arm, a comparator arm of either aspirin alone or short-term clopidogrel plus aspirin, and had a planned follow-up of at least one year. We focused our investigation on clopidogrel because findings from the DAPT trial suggested an increase in the risk of death and cancer death in that group; data on prasugrel are also presented as context for the clopidogrel findings.

<u>Investigation of the signal of increased all-cause death</u>

In the DAPT trial, extended use of clopidogrel plus aspirin was associated with a significantly increased risk of death (2.2% for 30 months vs. 1.5% for 12 months), whereas no increased risk was observed for prasugrel plus aspirin (1.6% for 30 months vs. 1.6% for 12 months).

The FDA trial-level meta-analysis included 12 trials[2-13] (56,799 patients) to explore the effect of clopidogrel on all-cause mortality. The incidence of all-cause mortality was 6.7% for the long-term clopidogrel plus aspirin arm and 6.6% for the comparator resulting in Mantel Haenszel Risk Difference (MH RD) = 0.04%, 95% confidence interval (CI) of (-0.35%-0.44%).

A similar meta-analysis that focused on the subset of 9 of these trials (45,374 patients) that enrolled patients with coronary artery disease or patients at risk of coronary artery disease also suggested no difference in the risk of all-cause mortality [MH RD of -0.07%, 95% CI (-0.43%-0.29%].

<u>Investigation of the signal of increased risk of cancer death</u>

In the DAPT trial, the risk of cancer reported as an adverse event was not different between the 30-month (2.4% ) and 12-month (2.3%) groups receiving clopidogrel when considering cancers reported after enrollment (from month 0 to 33 of the study). We performed several analyses of the cancer adverse event data, including "new" cancers in patients with no history of cancer or a history of cancer in a location different than the reported adverse event, and by cancer site. The relative risk of cancer for the 30-month vs. 12-month arm in the clopidogrel group ranged from 0.95 to 1.2, depending on the analysis. Analyses of time to first reported cancer adverse event demonstrated a hazard ratio of 1.06, 95% CI (0.80-1.41) for all cancer and 0.95, 95% CI (0.70-1.28) for new cancer. Similar analyses for the prasugrel group resulted in relative risks of cancer-related adverse events ranging from 1.4 to 1.6, and hazard ratios of 1.51, 95% CI (0.97-2.36) for all cancer and 1.51, 95% CI (0.96, 2.40) for new cancer. The patterns of the reported cancer sites did not suggest site-specific effects.

Despite no increase in the risk of cancer-related adverse events for clopidogrel in the 30-month arm of the DAPT trial, the risk of cancer-related death was increased compared to the 12-month arm (0.7% for 30 months vs. 0.2% for 12 months). In contrast, for prasugrel there was a trend towards a higher risk of cancer adverse events in the 30-month arm compared to the 12-month arm (see above), but the risk of cancer death was identical in both study arms (0.4% vs. 0.4%). These findings are difficult to reconcile.

To explore the cancer signal for clopidogrel in clinical trials other than the DAPT study, FDA performed two trial-level meta-analyses. The first was an analysis of cancer-related adverse events from four trials with information on cancer adverse events[2-5] (37,835 patients) that compared long-term use of clopidogrel and aspirin to use of either aspirin alone or short-term clopidogrel plus aspirin. The incidence of cancer adverse events was 4.2% for the long-term clopidogrel plus aspirin vs. 4.0% for the comparator. There was no apparent difference in the incidence of cancer adverse events between patients who received long-term clopidogrel plus aspirin and control patients across the four trials [MH RD = 0.19%, 95% CI (-0.2%-0.59%)].

The second trial-level meta-analysis was performed to assess cancer-related death and included five trials with information on cancer deaths[2-6] (40,855 patients). The incidence of cancer death was 0.9% for the long-term clopidogrel plus aspirin group vs. 1.1% for the comparator. There was no apparent difference in the incidence of cancer deaths between the long-term clopidogrel plus aspirin and control groups across the five trials [MH RD = -0.14%, 95% CI (-0.33%-0.06%)].

The findings from the DAPT trial with regard to cancer-related adverse events (increased for long-term prasugrel, but not for long-term clopidogrel) and cancer-related death (increased for long-term clopidogrel, but not for long-term prasugrel) have not been observed in our analyses of other randomized-controlled clinical trials. FDA's trial-level meta-analyses of other trials performed to evaluate the potential signal from DAPT do not suggest an increased risk of cancer adverse events or cancer-related death associated with long-term clopidogrel therapy.

Conclusion

Our reviews found no evidence of either a harmful or beneficial effect of clopidogrel on overall mortality in a population with, or at risk for, coronary artery disease, and no effect on cancer.

**References**


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