CLINICAL RESEARCH STUDY

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The Effect of Combined Aspirin and Clopidogrel Treatment on Cancer Incidence

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ABSTRACT

BACKGROUND: Multiple studies have shown an association between aspirin treatment and a reduction in newly diagnosed cancer. Conversely, there are conflicting clinical and laboratory data on the effect of combined clopidogrel and aspirin therapy on cancer incidence, including analyses suggesting an increased cancer risk. No large-scale cohort study has been performed to address this issue in a heterogeneous real-world scenario. We investigated the effect of clopidogrel and aspirin on cancer incidence compared with aspirin alone and no antiplatelet therapy.

METHODS: A population-based historical cohort study of subjects aged ≥50 years covered by Clalit Health Services, an Israeli health maintenance organization, was performed. Patients treated with the newer antiplatelet drugs, prasugrel or ticagrelor, which, like clopidogrel, inhibit adenosine diphosphate receptors, and those with prior cancer were excluded. Prescription records of antiplatelet medication were retrieved.

RESULTS: The cohort included 183,912 subjects diagnosed with 21,974 cancer cases based upon the International Classification of Diseases, Ninth Revision. Dual aspirin and clopidogrel was prescribed in 9.6%, while 49% received aspirin alone and 41% used neither. Compared with nonusers, there was a lower risk of cancer in subjects exposed to aspirin with (hazard ratio [HR] 0.46; 95% confidence interval [CI], 0.44-0.49) or without clopidogrel (HR 0.54; 95% CI, 0.52-0.56), on long-term follow-up. Combined treatment was associated with a lower cancer risk than the aspirin-only group (HR 0.92; 95% CI, 0.86-0.97).

CONCLUSIONS: Dual clopidogrel and aspirin treatment is safe regarding the cancer risk. This study generates the hypothesis that clopidogrel may reduce cancer incidence.

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KEYWORDS: Antiplatelet; Aspirin; Cancer; Clopidogrel

Aspirin treatment is associated with a reduction in cancer incidence, morbidity, and mortality, as shown in multiple studies across a wide variety of cancer types.[1-4] Recent guidelines even recommend low-dose aspirin use for the prevention of colorectal cancer in high-risk patients, as well as for prevention of cardiovascular disease in a subset of patients with a favorable risk—benefit profile.[5] The main theories attempting to explain these findings are based on the antiplatelet, anti-inflammatory,[6,7] and proapoptotic effects[8-10] of aspirin, among others.[11] The proposed antiplatelet effect of aspirin on cancer as well as the role of platelets in the natural history of cancer[6] suggest that other antiplatelet drugs may have a similar effect. One such drug, clopidogrel, is an irreversible thienopyridine prodrug inhibiting the P2Y12 subtype of adenosine diphosphate receptors critical for platelet activation.[12] While laboratory data suggest an anticancer effect of clopidogrel,[13,14] surprisingly, only a handful of contradictory analyses, all in the

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setting of ischemic heart disease, have examined the clinical effect of clopidogrel (mostly combined with aspirin) on cancer, demonstrating a negative,[15] positive,[16] or no effect[17,18] on cancer.

In view of these conflicting findings, we aimed to investigate the effect of the widely prescribed combination of clopidogrel and aspirin treatment on cancer incidence. Cancer incidence with combined antiplatelet therapy was compared with that of aspirin alone or no antiplatelet treatment in a real-world setting by means of a population-based historical cohort study.

CLINICAL SIGNIFICANCE

- Aspirin and clopidogrel reduced cancer risk compared with aspirin only or no treatment.
- This effect was seen across a wide range of malignancies, on long-term follow-up.
- The combination of aspirin and clopidogrel is safe and may even reduce cancer risk.

MATERIALS AND METHODS

Data Source

A population-based historical cohort study was performed, including individuals medically insured by Clalit Health Services (CHS), the largest health maintenance organization in Israel, providing care for over 4 million Israeli citizens. CHS has a comprehensive integrated electronic medical database, encompassing all medical information obtained prospectively at primary care and specialist clinics, pharmacies, laboratories, and during hospital admissions over more than a decade to date. Diagnoses are captured in the registry by means of diagnosis-specific algorithms, using code reading (eg, International Classification of Diseases, Ninth Revision [ICD-9]), text reading, laboratory test results, and disease-specific drug usage. Moreover, data can be accessed at the level of the individual patient facilitating rigorous large-scale studies.[19-21]

Study Population

In the current study, all CHS members living in the Sharon-Shomron district (accounting for more than 50% of the district's population) aged 50 years or older were included in the study cohort between January 2000 and January 2012, and followed until death, a diagnosis of cancer, or December 2014, whichever came first. The lag between the last date of inclusion and the end of the study period enabled a potential of at least 3 years of follow-up. We excluded patients treated with the newer adenosine diphosphate receptor inhibitors, prasugrel or ticagrelor, for any duration at any stage. Patients diagnosed with cancer prior to or within 1 year of study inclusion were also excluded, as it is unlikely that appearance of cancers diagnosed within the first year of antiplatelet treatment could have been influenced by antiplatelet medication.[2,22,23] Cancer was defined as the presence of one of the corresponding ICD-9 diagnoses. Different types of cancers were grouped, taking into account that the strongest evidence exists for gastrointestinal malignancies and colorectal cancer in particular. The study was approved by the institutional ethics committee in accordance with the Declaration of Helsinki.

Exposure Data

The main predictor in the current study was the type of antiplatelet treatment that the patients received during the study period. The cohort was initially divided into 4 groups based on antiplatelet treatment with aspirin, clopidogrel, both, or neither. Aspirin alone or clopidogrel-only treatment was defined as $\geq$1 monthly prescription for daily treatment at doses of 75 mg/100 mg or 75 mg, respectively, at any stage during the study period, but no prescription of the other drug. The combined antiplatelet treatment encompassed patients receiving both aspirin and clopidogrel treatment as defined above, but not necessarily simultaneously. Those patients never receiving aspirin or clopidogrel after the index date were considered nonusers. After a preparatory analysis, the clopidogrel-only group was subsequently excluded from analysis as discussed below, due to a low number of subjects receiving clopidogrel alone (**Table 1**). The long-term effect of antiplatelet therapy on the primary outcome was evaluated by stratifying for duration of follow-up. Long-term follow-up was defined as $\geq$5 years since the first antiplatelet dose in the treatment groups or the index date for nonusers, based upon prior studies.[23] Duration of antiplatelet exposure (ie, antiplatelet treatment duration) was determined by the time elapsed between first and last prescription of each antiplatelet agent, during each treatment period.

Covariates

Sex, age, body mass index (BMI), and smoking status were determined from the records closest to the index date.

Statistical Analysis

The primary endpoint was time until first diagnosis of cancer. Cancer was defined as any ICD-9 code corresponding with any type of malignancy, excluding nonmelanoma skin cancers.[24] We used the Cox proportional hazards regression model to determine the cancer risk under different antiplatelet treatments adjusting for age, sex, BMI, and smoking status. To account for variations in duration of aspirin treatment, aspirin treatment duration was added to this regression model, when comparing the aspirin-only group with the group receiving aspirin and clopidogrel. We then considered all patients who received at least 5 years of antiplatelet treatments and applied a binary regression model to estimate the risk for different subgroups of cancer. Under this model, the Exp(β) was

used to calculate the hazard ratio (HR) and the 95% confidence interval (CI) around it. Statistical analyses were performed using the SPSS software (version 23, SPSS Inc, Chicago, Ill).

RESULTS

Study Cohort

The preliminary study cohort included 184,781 patients with a median age of 54.9 years (50-100.1), 53.7% of whom were female. Based on exposure to antiplatelet drugs, patients were grouped as follows: no antiplatelet treatment, 75,624 (41%); clopidogrel only, 869 (0.4%); aspirin only, 90,615 (49%); clopidogrel and aspirin, 17,673 (9.6%). Compared with patients receiving no treatment, patients treated with antiplatelet drugs were older, had higher BMI, and were more likely to be men and smokers ($P < .001$ for all; Table 1). As expected, the group of patients fulfilling inclusion criteria and receiving clopidogrel alone was several orders of magnitude smaller than the other treatment and control groups (N = 869 overall, while only 271 had long-term follow-up after treatment). This precluded a meaningful unbiased comparison with the other groups and therefore, this group was excluded from analysis in the preanalytical feasibility stage of the study. Thus, the final analysis cohort included 183,912 subjects treated with aspirin, either alone or with clopidogrel, as well as nonusers. The respective median follow-up periods from study inclusion and from antiplatelet treatment until censorship are detailed in Table 2. Of note is a shorter median duration of follow-up in the no-antiplatelet group (119 months) compared with 155 and 179 months in the aspirin-only and dual antiplatelet groups, respectively. Long-term follow-up from antiplatelet therapy (≥5 years since the first antiplatelet dose) was available for 71% of those who used aspirin alone and 85% of combined aspirin and clopidogrel users. When examining long-term follow-up data, patients in the combined antiplatelet group were exposed to a longer average duration of aspirin (115 months) than aspirin-only users (85 months), in addition to 32.3 months of clopidogrel. There were 21,974 incident cases of newly diagnosed cancer throughout the study period (Table 2), the majority of which were solid malignancies (87%, n = 19,151), while the remainder were hematological malignancies (13%, n = 2823). Breast (13.3%, n = 2925), colorectal (13.7%, n = 3020), prostate (9.5%, n = 2090), and lung cancer (7.4%, n = 1628) were the most common cancer types, while 21.7% (n = 4762) of all malignancies were gastrointestinal. The most incident hematological malignancy was non-Hodgkin's lymphoma (4.3%, n = 943).

Antiplatelet Therapy and the Risk of Malignancy

In the primary study analysis, long-term (≥5 years) follow-up from antiplatelet treatment with aspirin alone or combined with clopidogrel was associated with a lower risk of cancer, compared with no antiplatelet treatment (Table 2). Aspirin use alone or in combination with clopidogrel was associated with a 46% (HR 0.54; 95% CI, 0.52-0.56, $P < .001$) and 54% (HR 0.46; 95% CI, 0.44-0.49, $P < .001$) reduction in incident cancer, respectively, after adjustment for covariates. On long-term follow-up, patients receiving dual aspirin and clopidogrel treatment had a lower risk of cancer than the aspirin-only group, after adjustment for baseline variables and duration of aspirin treatment (HR 0.92; 95% CI, 0.86-0.97, $P = .006$) (Table 3). When these analyses were stratified for cancer site, the reduction in cancer incidence with combined antiplatelet therapy compared with aspirin alone was maintained in solid cancers (Table 4). There was a lack of effect of combined therapy compared with aspirin alone in preventing hematological cancer (Table 4). Antiplatelet treatment was also associated with a lower risk of newly diagnosed cancer ($P < .001$), compared with patients who received no treatment, with any duration of follow-up, on multivariate analysis (Table 2).

DISCUSSION

This is the first large-scale cohort study specifically addressing the effect of dual clopidogrel and aspirin treatment on the incidence of cancer in a real-world setting, whereby dual treatment was associated with a 8% reduction in cancer incidence in comparison with aspirin alone. In the combined therapy group, clopidogrel therapy was administered for a potentially clinically relevant duration of just below 3 years, on average. Moreover, the advantage of the dual therapy group over the aspirin-only group was apparent even after adjustment for duration of aspirin therapy. This

Table 1 Baseline Characteristics According to Antiplatelet Treatment Group

Characteristic	Aspirin Only	Aspirin and Clopidogrel	Clopidogrel Only	No Antiplatelet Treatment	Total
No. of participants	90,615	17,673	869	75,624	184,781
Age in y (SD)	61.5 ± 11.4	60.9 ± 9.8	62.3 ± 10.7	57.2 ± 10.9	59.8 ± 11.3
Female (%),	49,802 (55)	5801 (32.8)	415 (47.8)	43,263 (57.2)	99,281 (53.7)
Male (%)	40,813 (45)	11,872 (67.2)	454 (52.2)	32,361 (42.8)	85,500 (46.3)
Mean BMI (cm/m^2)	31.9 ± 8.7	32.4 ± 9.2	30.8 ± 8.2	29.5 ± 7.3	31.0 ± 8.3
Ever smoker (%)	17,856 (19.7)	5557 (31.4)	156 (18)	12,648 (16.7)	36,217 (19.6)

BMI = body mass index; SD = standard deviation.

Table 2 The Risk of Cancer in Subjects Treated with Aspirin or Both Aspirin and Clopidogrel, Compared with No Antiplatelet Treatment

		Long-Term Follow-Up†		All Durations of Follow-Up	
	No Antiplatelet (n = 75,624)	Aspirin Only (n = 64,362)	Aspirin and Clopidogrel (n = 15,103)	Aspirin Only (n = 90,615)	Aspirin and Clopidogrel (n = 17,673)
Cancer during follow-up, % (n)	11.7 (8816)	8.8 (5692)	8.5 (1286)	12.6 (11,388)	10.0 (1770)
No. of cancer cases/1000 patient years	12.8	7.6	7.0	12.0	8.5
Median duration of follow-up (range), mo‡	119 (12-179)	179 (12-179)	179 (12-179)	155 (12-179)	179 (12-197)
Median duration of follow-up since initiation of antiplatelet treatment (range), mo§	NA	118 (60-178)	135 (60-178)	93 (1-178)	124 (1-178)
Mean duration of antiplatelet treatment (months ± SD), mo	NA	85.1 ± 51.7	Aspirin: 115 ± 42.4; Clopidogrel: 32.3 ± 39.3	66.3 ± 53.4	Aspirin: 99.0 ± 50.1; Clopidogrel: 29.8 ± 37.4
Risk of cancer‖, HR (95% CI)					
Unadjusted	1 (ref.)	0.48 (0.46-0.49)*	0.40 (0.37-0.42)*	0.91 (0.89-0.94)*	0.64 (0.61-0.67)*
Adjusted for: age, sex, BMI, smoking status	1 (ref.)	0.54 (0.52-0.56)*	0.46 (0.44-0.49)*	0.76 (0.74-0.78)*	0.49 (0.47-0.52)*

BMI = body mass index; CI = confidence interval; HR = hazard ratio; NA = not applicable; SD = standard deviation.
*P <.001.
†More than 5 years follow-up from first antiplatelet or entering study cohort (for reference group).
‡Time elapsed between study inclusion and censorship.
§Time elapsed between first prescription of antiplatelet treatment and censorship.
‖Compared with no antiplatelet treatment.

supports the hypothesis that exposure to clopidogrel may be associated with a reduction in incident cancer. The beneficial effects of aspirin are most evident on long-term follow-up (often defined as ≥3 or 5 years),[2,22,23] and the same was assumed regarding the effect of combined therapy. Our analysis was designed accordingly, and similarly demonstrated a larger reduction in cancer incidence in the group with long-term follow-up. The shorter follow-up in the no-

Table 3 Long-Term Risk of Cancer with Combined Aspirin and Clopidogrel Treatment vs Aspirin Alone*

	Aspirin Only* (n = 64,362)	Aspirin and Clopidogrel Treatment* (n = 15,103)
Cancer during follow-up, % (n)	8.8 (5692)	8.5 (1286)
No. of cancer cases/1000 patient years	7.6	7.0
Median duration of follow-up (range), mo†	179 (12-179)	179 (12-179)
Median duration of follow-up since initiation of antiplatelet treatment (range), mo‡	118 (60-178)	135 (60-178)
Mean duration of antiplatelet treatment (months ± SD), mo	85.1 ± 51.7	Aspirin: 115 ± 42.4; Clopidogrel: 32.3 ± 39.3
Risk of cancer, HR (95% CI)		
Unadjusted	1 (ref.)	0.89 (0.84-0.95)
Age, sex, BMI, smoking status	1 (ref.)	0.79 (0.74-0.84)
Age, sex, BMI, smoking status, duration of aspirin treatment§	1 (ref.)	0.92 (0.86-0.97)

BMI = body mass index; CI = confidence interval; HR = hazard ratio; SD = standard deviation.
*More than 5 years follow-up from first antiplatelet prescription.
†Time elapsed between study inclusion and censorship.
‡Time elapsed between first prescription of antiplatelet treatment and censorship.
§Determined by the time elapsed by first and last monthly aspirin prescription for each treatment period.

Table 4 The Risk of Subgroups of Cancer in Subjects Treated with Aspirin or Both Aspirin and Clopidogrel on Long-Term Follow-Up*

	Type/Site of Malignancy	No Antiplatelet	Aspirin Only	Aspirin and Clopidogrel	
No. of cancer cases/1000 patient years (Total number of cancer cases)	Hematological (n = 1963)†	1.62 (1035)	1.1 (745)	1.1 (183)	
	Solid (n = 13,831)	11.4 (7781)	6.7 (4947)	6.1 (1103)	
	Gastrointestinal (n = 3485)‡	3.1 (2017)	1.7 (1213)	1.5 (255)	
	Colorectal cancer (n = 2154)	1.9 (1272)	1.1 (739)	0.8 (143)	
	Nongastrointestinal (n = 10,346)	8.6 (5764)	5.1 (3734)	4.7 (848)	
			vs No Antiplatelet§	vs No Antiplatelet§	vs Aspirin Only§,‖
Risk of cancer, HR (95% CI)	Hematological†	1 (ref.)	0.72 (0.65-0.795)	0.69 (0.58-0.81)	0.93 (0.78-1.1)
	Solid	1 (ref.)	0.59 (0.55-0.64)	0.47 (0.45-051)	0.85 (0.79-0.92)
	Gastrointestinal‡	1 (ref.)	0.64 (0.62-0.66)	0.57 (0.53-0.61)	0.82 (0.71-0.94)
	Colorectal cancer	1 (ref.)	0.58 (0.53-0.63)	0.45 (0.38-0.54)	0.77 (0.64-0.92)
	Nongastrointestinal	1 (ref.)	0.66 (0.63-0.69)	0.6 (0.55-0.65)	0.87 (0.80-0.94)

CI = confidence interval; HR = hazard ratio.
*More than 5 years follow-up from first antiplatelet or entering study cohort (for reference group).
†Including: acute leukemia, multiple myeloma, myeloproliferative neoplasms, lymphoproliferative disorder, myelodysplastic syndrome.
‡Including malignancies of: colon or rectum, esophagus, liver or bile ducts, pancreas, gastric.
§Adjusted for: age, sex, body mass index, smoking status.
‖Adjusted for duration of aspirin therapy.

antiplatelet group may be due to the higher rate of malignancy and early censorship in this group. In addition, many patients start antiplatelet therapy as they age (as reflected by the age differences between the antiplatelet and no-antiplatelet groups), shortening the potential follow-up time for subjects in this older group, as these patients would then be included in one of the antiplatelet groups once they begin this treatment. These differences in follow-up were accounted for by the Cox proportional hazards model, and cancer incidence rates are accordingly presented as cases per patient-years at risk. The beneficial effect of the 2 antiplatelet treatment groups on cancer incidence was observed across various types of solid cancers. This is similar to prior studies showing a reduction in cancer incidence, morbidity, and mortality with aspirin treatment, across a wide variety of cancers.[2,4,25,26]

When considering these results, one should bear in mind that the fact that a drug has an antiplatelet effect, even via the same target (eg, P2Y12 receptor), does not ensure a uniform effect on cancer.[15,27-31] In the CAPRIE trial, the overall rate of new solid cancers was similar for clopidogrel monotherapy vs that with aspirin,[17] with a possible early decrease in the clopidogrel arm and subsequent increase on long-term follow-up.[11] This is compatible with the proposed concept that clopidogrel may be protective against cancer.[32] Furthermore, the CHARISMA trial demonstrated a lower rate of new cancers as well as less cancer-related mortality in the combined aspirin and clopidogrel group when compared with aspirin monotherapy.[16] Subsequently, the Dual Antiplatelet Therapy (DAPT) study compared extended dual antiplatelet therapy (aspirin with either clopidogrel or prasugrel) with aspirin and placebo after 1 year of dual antiplatelet therapy after placement of a drug-eluting coronary artery stent.[15] This study in fact showed an increase in cancer-related death, raising concern over a possible delayed effect of clopidogrel or combined antiplatelet therapy on cancer, despite limitations of this analysis. Reassuringly, a recent US Food and Drug Administration meta-analysis of this and other studies showed no increase in cancer incidence or in cancer-related death among patients receiving aspirin and clopidogrel.[18] Similarly, a recent population-based cohort study of colorectal, breast, and prostate cancer patients found no evidence of an increased risk of cancer-specific mortality among users of postdiagnostic clopidogrel.[33] The latest data, together with the findings in our study, represent a shift in the contemporary evidence toward the concept that combined aspirin and clopidogrel therapy is most probably safe with regard to cancer incidence and mortality.

The findings in our study regarding clopidogrel are biologically plausible in view of a handful of recent murine cancer models suggesting that antiplatelet P2Y12 inhibitors positively influence the natural history of cancer, without clarifying the mechanism thereof.[13,14,34] In a murine pancreatic cancer model with induced thrombosis, clopidogrel reduced tumor size and metastasis and also reduced p-selectin expression at the site of injury.[14] Similarly, single-agent clopidogrel and aspirin treatment prevented or delayed development of hepatocellular carcinoma in a mouse model of chronic hepatitis B and improved survival.[13] The common denominator between the mechanisms of these 2 drugs is their antiplatelet effect, which generates data supporting the antiplatelet hypothesis,[6] while not ruling out a contributory role of other mechanisms.[7] Whether clopidogrel's effect is by deeper antiplatelet inhibition or by a class-specific effect such as the proposed pleotropic effects of platelet P2Y12 inhibitors[35] remains a topic for future research. Furthermore, mild platelet inhibition by aspirin or P2Y12 inhibitors may somehow interfere with diverse processes in the natural history of cancer, possibly differentially affected by different antiplatelet treatments.[36]

The main limitations of our study are those inherent to the design of a retrospective analysis of prospectively assimilated data. However, misclassification of treatment group, especially with regard to clopidogrel treatment, is unlikely due to the following reasons: 1) clopidogrel is a prescription drug; 2) only drugs acquired without prescription from small private pharmacies would not be automatically captured in the CHS database; 3) patients will not be reimbursed for clopidogrel not acquired through this system. Although the possibility of over-the-counter aspirin use cannot be ruled out, this wouldn't explain the difference between the aspirin-only and combined antiplatelet group, and would be registered if bought together with other chronic drugs, such as clopidogrel. Some risk factors for cancer, such as diet, occupation, and family history, were not registered in this cohort, possibly confounding the results. Therefore, it remains a possibility that these and other unknown factors may have mediated the impressive decrease in cancer incidence seen with combined antiplatelet therapy, rather than a true drug effect. Nevertheless, most major risk factors were registered and accounted for in multivariate analysis. In fact, patients receiving dual antiplatelet treatment had more identifiable risk factors for cancer, thus strengthening our findings. Another limitation of this study is the lack of separate sub-analyses of the effect of combined antiplatelet therapy on most of the major cancer types (eg, lung, breast, and prostate cancer). There is, however, a sub-analysis of solid cancer, gastrointestinal malignancies, and importantly, colorectal cancer, where the most evidence for an anticancer effect of aspirin exists. Finally, our study was not designed to assess the short-term effect (ie, <5 years of follow-up) of dual antiplatelet therapy on cancer incidence. The focus of our study was placed upon long-term follow-up, as evidence of aspirin's beneficial effects on cancer is strongest for long-term therapy/follow-up,[2,22,23] and because the recent concern over deleterious effects on cancer with dual therapy was larger when discussing longer terms of follow-up.[11] Strengths of our study include the magnitude of the sample size, the real-world setting, heterogeneity regarding antiplatelet treatment indications, the clear delineation of duration of exposure to each drug by an objective measure (ie, prescription use), and sub-analyses accounting for duration of aspirin treatment and length of follow-up.

In conclusion, this study shows that combined aspirin and clopidogrel use is at least as safe as prolonged aspirin use with regard to cancer incidence, and generates the hypothesis that clopidogrel may reduce cancer incidence. This, along with a recent analysis by the Food and Drug Administration[18] goes a long way toward allaying recent concern[15] about the effect of combined antiplatelet treatment on cancer incidence. We eagerly await more clinical and basic research about the anticancer effect of clopidogrel and other newer antiplatelet agents.

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