Cancer event rate and mortality with thienopyridines: A systematic review and meta-analysis

Author Affiliations

[1] Keele Cardiovascular Research Group, Keele University, Stoke-on-Trent, UK

[2] Oxford University Clinical Academic Graduate School, Oxford University, Oxford, UK

[3] Department of Cardiology, Royal Stoke Hospital, Stoke-on-Trent, UK

[4] University Hospital of Wales, Cardiff, UK

[5] Freemans Hospital and Institute of Cellular Medicine, Newcastle University, Newcastle-Upon-Tyne, UK

Rafail Angelos Kotronias,[1,2] *Academic Foundation Trainee*

Chun Shing Kwok,[1,3] *Cardiology Registrar and Academic Clinical Fellow in Cardiology*

Chun Wai Wong,[1] *Medical Student*

Tim Kinnaird,[4] *Consultant Cardiologist*

Azfar Zaman, [5] *Professor of Cardiology*

Mamas A Mamas,[1,3] *Professor of Cardiology*

Correspondence to: Rafail A Kotronias

Email: rafailkotronias@gmail.com

Tel: 01782 671653

Fax: 01782 674467

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ABSTRACT

Introduction: Thienopyridines are a class of antiplatelet drugs widely used in cardiovascular disease prevention and treatment. There is recent concern regarding the safety of thienopyridines because of possible malignancy risk. Therefore, we performed a systematic review and meta-analysis to evaluate the association between thienopyridine exposure and malignancy.

Methods: We searched MEDLINE and EMBASE in March 2016 for studies which evaluated incident cancer and cancer mortality with and without exposure to thienopyridines. Relevant studies were identified, data were extracted and analysed with random effects meta-analysis.

Results: A total of 9 studies (6 randomised controlled trials and 3 cohort studies) with 311,595 participants were included. The cancer event rate during the study period with clopidogrel and prasugrel was 1.56%. When compared to standard aspirin or placebo, thienopyridines are not significantly associated with cancer mortality and event rate OR 1.12 [95% CI 0.80-1.56, n=3] and OR 0.92 [95% CI 0.52-1.64, n=2] respectively. Further analyses examining clopidogrel only showed no significant association with cancer event rate or malignancy related death. When comparing prasugrel to clopidogrel no significant association was noted for cancer event rate OR 1.10 [95% CI 0.89-1.37, n=2]. Subanalyses according to cancer location showed that thienopyridines are not significantly associated with malignancy mortality and/or incidence.

Conclusions: Our results suggest that there is currently insufficient evidence to suggest that thienopyridine exposure is associated with an increased risk of cancer event rate or mortality.

Key points:

- Cancer-related mortality is not linked to thienopyridines with contemporary data
- Standardisation of cancer-end points in trials will reduce adjudication bias
- Cohort studies can be used to supplement trial findings due to longer follow-up

1. INTRODUCTION

Thienopyridines - ticlodipine, clopidogrel and prasugrel – are adenosine diphosphate $P2Y_{12}$ platelet receptor inhibitors that reduce platelet activation. Their widespread use in cardiovascular medicine owes much to the pivotal role that platelet activation has in the pathophysiology of many cardiovascular diseases such as myocardial infarction, stroke and peripheral vascular disease (1). Due to their favourable profile, thienopyridines - mainly clopidogrel and recently prasugrel - are increasingly used in the treatment and secondary prevention of acute coronary syndrome (2–5), cerebrovascular accidents (6–8) and other peripheral vascular disease (9,10). Despite their efficacy in reducing major adverse cardiovascular events, secondary analyses of two randomised controlled trials raised concerns of a potential interplay between increased incidence of cancer and cancer-related death with thienopyridines (11,12).

The Dual Antiplatelet Therapy (DAPT) study of 11,648 patients compared the effects of continued thienopyridines versus placebo beyond 12 months in patients who underwent PCI (12) reported that at 33 months follow-up the cancer incidence event rate was higher in the continued thienopyridine group (2.0% vs 1.6%, p=0.12), whilst cancer-related mortality was significantly higher in the continued thienopyridine group (0.6% vs 0.3%, p=0.02). However, the latter was not significant once cancer prior to enrolment was excluded from the analysis. Conversely, the CHARISMA randomized controlled trial in 15,603 patients (13), after adjusting for relevant confounders, showed a reduced, though not statistically significant reduction in cancer-related mortality with aspirin and clopidogrel [aHR 0.854, 95% CI 0.588-1.240] at 30 months. Similarly, a retrospective observational cohort study of clopidogrel exposure in a cohort of 41,403 newly diagnosed patients with colorectal,

breast and prostate cancer influenced cancer-related mortality reported (after adjusting for relevant confounders), no significant differences in cancer related mortality for colorectal cancer [aHR 0.98, 95% CI 0.77-1.24, breast cancer [aHR 1.22, 95% CI 0.90-1.65] or prostate cancer [aHR 1.03 95% CI 0.82-1.28] (14).

A systematic review by Serebruany et al. studying the incidence of solid cancers with antiplatelet therapy reported an association between long exposure to antiplatelet therapy and increased risk of new solid cancers and cancer-related mortality, though the evidence was not sufficient to alter current practice (15). However, the systematic review examined a broad topic, including a limited number of heterogeneous studies without a statistical meta-analysis. Moreover, since the original review, newer studies have been published increasing the evidence base available for analysis. The aim of this report is to perform a systematic review and meta-analysis of more contemporary studies and trials to assess whether thienopyridines increase the risk of cancer events and malignancy related deaths.

2. METHODS

2.1 Search Strategy

We searched MEDLINE and EMBASE in February 2016 using the broad search terms: ((Thienopyridine OR prasugrel OR ticlopidine OR clopidogrel OR ticagrelor) AND (Cancer OR carcinoma OR malignancy OR malignant OR neoplasm OR tumour OR tumor)). The coverage dates for the former were from 1946 to February 2016 and for the latter from 1974 to 29th of February 2016. No language restrictions were applied, and translations were not required.

2.2 Study selection

The abstract and titles yielded by the search were screened by two independent investigators (RAK, CWW) against the inclusion criteria. Additional studies were retrieved by checking the bibliography of included studies and relevant reviews. The full text of the studies that appeared to have met inclusion criteria, were independently screened by RAK and CWW at least once, to confirm eligibility for inclusion. The results were combined and subsequently reviewed by an experienced reviewer (CSK). Disagreements were resolved by consensus after consultation with MAM.

2.3 Eligibility Criteria

We included primary studies that reported on malignancy event rate or malignancy related mortality after thienopyridine administration. Risk of publication bias was minimized by inclusion of conference abstracts or presentations which met the inclusion criteria. We excluded studies that evaluated malignancy rates of ticlodipine and ticagrelor because the former is no longer clinically used and the latter is not strictly a thienopyridine. Additionally, comments, reviews and case reports were excluded from the final analysis. When duplicate reports of the same study were identified, only the report with the most complete dataset and detailed methodology description was included.

2.4 Data Collection

Data were extracted independently by two investigators (RAK, CWW) from each study into preformatted tables generated in Microsoft Word. Data abstracted included information on the year, country, number of participants, participant inclusion criteria, evaluated antiplatelets, and cancer outcomes and follow-up. To

assess the quality of the included studies we used the Cochrane Collaboration's Tool for assessing risk of bias in randomised controlled trials (RCTs) (16) and the Newcastle-Ottawa scale to assess the quality of non-randomised studies (17). For studies where outcome data were not available in the primary publication, the appendices, other peer-reviewed systematic reviews and Food and Drug Administration (FDA) reports were searched for available data. No study investigators were contacted for additional information as data were available for all included studies. Disagreements were resolved by consensus after consultation with MAM.

2.5 Data Analysis

On the basis of the availability of data, we synthesized the results using meta-analysis with quantitative pooling, graphically, or by narrative synthesis. Random and fixed effects meta-analyses were performed by the Mantel-Haenszel method for dichotomous data using RevMan 5.3 (Nordic Cochrane Centre, København, Denmark) in order to estimate pooled risk ratios. Statistical heterogeneity was assessed using I^2 statistic, The method of pooling has been previously described (18). We performed analyses examining cancer event rate and malignancy-related mortality. Additionally, we performed sensitivity analysis to detect cancer events rate or cancer related mortality with clopidogrel only, also comparing clopidogrel to prasugrel.

3. RESULTS

A total of 9 studies met the inclusion criteria; 6 randomised controlled trials (12,13,19–22) and 3 retrospective cohort studies (14,23,24). The total number of participants reached 311,595; varying from 3,479 (23) to 184,871 (24). The process of

study selection is presented in Figure I. Data on study design, participant number, inclusion criteria, antiplatelet drugs, the cancer specific follow-up and the outcome evalated are presented in Table I. Table II presents a descriptive quality assessment of the included studies and Table III the reported cancer outcomes per study.

Whilst all studies reported on clopidogrel, only two specifically reported on prasugrel (11,20,21), with a wide variety in the outcomes reported by each study; any cancer event rate, specific cancer event rate or even cancer related mortality. Cancer specific follow-up in RCTs ranged from a minimum of six months to a maximum of 33 months. Mean weighted follow-up for all studies that reported on follow up was 9.61 years (12,14,19,21,22,24), but upon exclusion of the cohort studies (14,24) mean weighted follow-up was 1.63 years. By contrast, cohort studies had a mean weighted follow-up of 10.55 years.

3.1 Cancer event rate

The results and quality assessment of studies are presented in Tables II and III. The cancer event rate was 1.56% with clopidogrel (11–14,19,21,22,24) and 1.56% with prasugrel (11,21). Thienopyridine exposure did not associate with increased odds of cancer events OR 0.92 [95% CI 0.52-1.64, n=2] (Figure II). This observation was retained in a sensitivity analysis with clopidogrel only OR 0.70 [95% CI 0.66-0.75, n=1] (Figure III). A further analysis comparing prasugrel to clopidogrel showed no significant difference in cancer event rate OR 1.10 [95% CI 0.89-1.37, n=2] (Figure IV). All the above relationships were maintained in fixed effects analysis.

3.2 Thienopyridines and cancer mortality

Analysis of studies reporting on cancer mortality indicate that thienopyridine treatment versus control or aspirin was not associated with an increased odds of mortality OR 1.12 [95% CI 0.80-1.56, n=3] (Figure V), a relationship maintained in clopidogrel only sensitivity analysis OR 0.85 [95% CI 0.59-1.24, n=1] (Figure III). An analysis comparing prasugrel and aspirin to clopidogrel and aspirin suggested no significant differences in the odds of cancer mortality (OR 1.57 [95% CI 0.91-2.71], n=1) (Figure IV). When compared to a random effects model, fixed effects meta-analysis highlighted no significant differences in the odds of cancer mortality with thienopyridines in RCTs OR 1.09 [95% CI 0.79, 1.49, n=2], despite a numerically different result.

3.3 Thienopyridine relation to cancer event rate by location

Data were available for all thienopyridines for lung, colorectal, breast, prostate and hepatocellular cancer. In the case of clopidogrel, data were also available for pancreatic and haematological cancers. After pooling all studies per cancer site thienopyridines and clopidogrel alone were associated with no significant differences in cancer event rate (Figure VI, VII) However, in the hepatocellular carcinoma subgroup clopidogrel showed a significant decrease in the risk of cancer OR 0.27 (95% CI 0.09-0.77, n=1). The comparison of clopidogrel with prasugrel showed no significant differences in the odds of site-specific cancer event rates (Figure VIII). Fixed effects meta-analysis did not reveal any differences to the random effects meta-analysis.

4. DISCUSSION

Our analysis suggests there is no evidence of a thienopyridine class effect in increasing cancer event rate or malignancy-related mortality when compared to standard aspirin or no drug. Subanalyses of cancer mortality and cancer event rates also analysed by type of medication showed no cancer signal. Indeed, our results support that the increased cancer mortality with thienopyridines is a chance finding, a hypothesis proposed by the DAPT and TRITON TIMI 38 study investigators (12,20). Furthermore, our study explores contemporary evidence to examine the thienopyridine-cancer hypothesis that has been put forward to explain the findings.

Our results are based on both RCTs and cohort studies. Our primary analyses are largely influenced by two, large, well-designed retrospective cohort studies with long-term follow-up of 5 and 12 years respectively. Hicks et al. (14) reported a statistically significant reduction in cancer mortality with thienopyridines aOR 0.63 [95% CI 0.55-0.73], whilst Leader et al. (24) a significant reduction in cancer event rate aOR 0.46 [95% CI 0.44-0.49]. Despite the use of multivariate analysis to adjust for potential confounders including but not limited to age, gender, smoking status and duration of treatment, results from retrospective cohort studies can be influenced by unmeasured confounders; limiting subsequent inferences. Our findings are in contrast to the DAPT trial findings which showed a statistically significant late increase in cancer mortality with prolonged dual antiplatelet therapy of aspirin and thienopyridines (0.3% vs 0.6%, p=0.02) (12). It must be noted, however, that in this study there was an imbalance of patients with pre-existing, occasionally metastatic, cancer between the two arms of the trial after randomisation (12). Additionally, a sub-analysis excluding cancers diagnosed prior to enrolment exonerated the increased risk of cancer mortality.

One possible mechanistic explanation for the previous excess of cancer is that dual antiplatelet drug regimens increase bleeding risk from pre-existing tumours, which in turn may lead to earlier tumour detection on the DAPT group; an observation that has been previously reported for anticoagulants and anti-platelets (25,26). Moreover, in support of this argument is that patients on anti-platelets have a lower rate of advanced stage (IV) colorectal carcinoma compared to the control arm; possibly due to detection of existing tumours at an earlier stage (27).

From a pathophysiological point of view, Serebruany et al. (15) hypothesised that antiplatelet medication could be responsible for the increase in cancer incidence owing to carcinogenicity of the drug and/or its components. However, this hypothesis is not supported by *in vivo* animal studies which showed that prasugrel and clopidogrel were not carcinogenic (11). Regarding the mechanisms underlying cancer mortality, Serebruany et al. also suggested that disruption of the platelet-tumour niche and the subsequent enhancement of metastatic dissemination might occur. However, laboratory evidence suggests that platelets have a pro-metastatic function by promoting epithelial to mesenchymal transition, modulating the pre-metastatic niche and assisting tumour cells to evade the immune system (28). Therefore, administration of thienopyridines should – in theory – reduce the risk of metastasis. In favour of this argument, a mouse model of lung metastasis showed that $P2Y_{12}$ deficient mice had less tumour burden (29). Therefore, evidence to date does not support a pathophysiological link between increased cancer mortality and thienopyridine treatment.

On an individual study level, only DAPT and TRILOGY included a specialist oncology adjudication committee to minimise ascertainment bias. The potential effect of ascertainment bias on cancer mortality and event rate given the small event rate is

important and is highlighted by a recent FDA consensus analysis (11). Moreover, sampling bias is an inherent methodological shortfall of the two cohort studies when compared to randomised trials. Indeed, the aforementioned weaknesses in individual study design could account for the statistical heterogeneity of our results and the residual confounding of their individual results. However, sub-group analyses including only RCTs for cancer event rate and cancer-mortality with thienopyridines (Figures II and V) showed that cohort studies did not alter the results significantly. Therefore, our results also benefit from the extended follow-up of the included cohort studies.

Our study is the first meta-analysis to address this contemporary and controversial topic using both prospective and retrospective studies. In an era of intense pharmacovigilance, our study seeks to clarify concerns raised by DAPT, especially when considering that cancer has overtaken cardiac events as the primary mortality cause after percutaneous coronary intervention (30,31). Additionally, the use of random effects model in our statistical analysis permits inferences of the results to the wider population.

Indeed, as with every meta-analysis, it is inherently limited by the quality of the included studies. First, the studies enrolled heterogeneous populations, had different study protocols and cancer-event adjudication, and compared different duration and combinations of antiplatelet therapies. However, the heterogeneity enables examination of different populations which would provide more in the way of identifying a phenomenon that affects a particular sub-population. Indeed, our fixed effects model analysis did not identify a specific at risk sub-population. Second, the safety (cancer event) end-point analyses in trials are observational in nature, conducted without a pre-specified hypothesis and the necessary power calculations,

predisposing individual studies to Type I error. To minimise these errors, study authors grouped various cancers together to increase the event rate and simplify the analysis construct; unavoidably limiting the pathophysiological rationale. However, our sensitivity analysis by cancer location yields similar results to the pooled analysis.

Interestingly, follow-up varied greatly from study to study with trials having shorter follow-up at risk of missing late cancers; a high possibility given the late cancer signal shown by the DAPT trial (12). However, the study by Hicks et al. with a median follow-up of 12.9 years showed an association of reduced cancer mortality with clopidogrel use (14). Though the included studies mainly examined clopidogrel, DAPT examined clopidogrel and prasugrel and has not published the dichotomised data to date. The use of aspirin in the comparison group in early trials could affect the results for clopidogrel, but the direction of this effect would likely lead to an overshooting of the odds ratio as several studies suggest that aspirin reduces cancer event rate and mortality (32–34). Indeed, later trials (CHARISMA, DAPT, TRILOGY) have included aspirin in both groups, but the influence of this addition on cancer event rate or mortality is unexplored (12,13,21).

5. CONCLUSIONS

To our knowledge, this is the first systematic review and meta-analysis to date examining whether thienopyridine antiplatelets increase cancer mortality and cancer events. We found the cancer event rate was 1.56% for both prasugrel and clopidogrel exposed patients. Our study does not support concerns for a class effect of thienopyridines in increasing cancer event rate and/or mortality when compared to standard aspirin or no drug.

Compliance with ethical standards

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CONFLICTS OF INTEREST: Rafail Angelos Kotronias, Chun Shing Kwok, Chun Wai Wong, Tim Kinnaird, Azfar Zaman, Mamas A Mamas have no conflicts of interest that are directly relevant to the content of this study.

Ethical approval was not required for the study.

Patient consent was not required for the study.

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Figure I: Flow diagram of study inclusion (35)

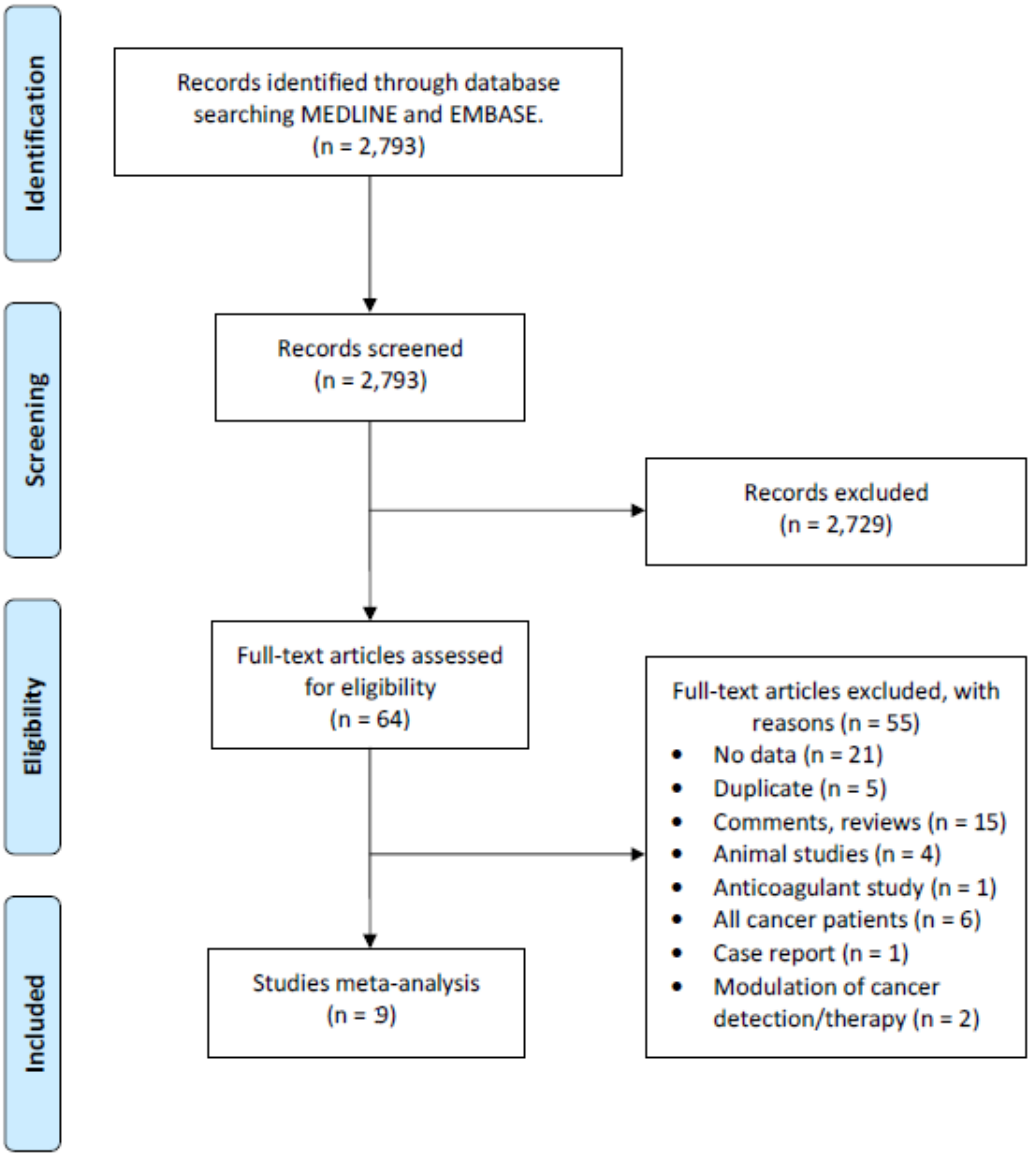

Table I: Study design, population, antiplatelet drugs evaluated and cancer outcomes

Study ID	Design;Country;Year	Total population	Participant inclusion criteria	Antiplatelet drugs evaluated	Cancer outcomes and follow up
CAPRIE trial (22)	RCT; International;1992-1995.	19,185 (CLOP n=9,599, ASA n=9,586).	Participants had ischaemic stroke, myocardial infarction or peripheral arterial disease.	CLOP, ASA.	Cancer event rate Mean follow up 1.63 years for lung cancer.
CHARISMA trial (13)	RCT; International; 2002-2003.	15,603 (CLOP/ASA n=7,802, placebo/ASA n=7,801).	Participants were ≥45 years oldand had multiple atherothrombotic risk factors, coronary disease, cerebrovascular disease, or peripheral arterial disease.	CLOP/ASA, placebo/ASA.	Cancer event rate and mortality Up to 30 month follow up for cancer events, cancer mortality and lung cancer events.
CURE trial (19)	RCT; International; 1998-2000.	12,562 (CLOP n=6,259, placebo n=6,303).	Participants were >60 years old with ECG changes or an elevation in the serum level cardiac enzymes or markers at study entry.	CLOP, placebo.	Cancer event rate Follow up 3 monthly until the end of the study for colorectal cancer and lung cancer.
DAPT Study (12)	RCT; International; 2009-2011.	11,648 (12 months of dual antiplatelet then randomized to ASA/Placebo n=5,786, dual antiplatelet ASA + anythienopyridine n= 5,862).	Participants were ≥18 year old with dual antiplatelet therapy after DES or BMS stent implantation.	Dual antiplatelet therapy for 12 months then aspirin or continued dual antiplatelet.	Cancer event rate and mortality Follow up from 30-33 months for all cancers, lung cancer, prostate cancer, pancreatic cancer, colorectal cancer and hematologic cancer.

Hicks 2015 (14)	Retrospective cohort study; UK; 1998-2009.	41,403 (Colorectal Cancer n=10,359, Breast Cancer n=17,889, Prostate Cancer n= 13,155).	Participants had breast, colorectal and prostate cancer diagnosed between 1998-2009.	CLOP.	Cancer mortality Average follow up 5 years for colorectal, breast and prostate cancer.
Leader 2015 (24)	Retrospective cohort study; Israel; 2000-2014.	184,871 (control n=75,624, CLOP only n=271, ASA only n=64,362, dual antiplatelet n=15,103).	Participants were ≥50 year old who did not have prasugrel, ticagrelor or cancer diagnosis.	CLOP only, ASA only, CLOP/ASA.	Cancer event rate Median follow-up 155 months for any cancer, solid cancers, gastrointestinal cancers, non-gastrointestinal cancers.
Lee 2015 (23)	Retrospective cohort study; South Korea; Unclear.	3,479 (no antiplatelet n=2,891, antiplatelet n=588).	Participants had chronic hepatitis B and HBV DNA completely suppressed with antiviral treatment.	ASA only, CLOP only, ASA/CLOP.	Cancer event rate Not specified follow up for hepatocellular carcinoma.
TRILOGY trial (21)	RCT; International; 2008-2011.	9,236.	Participants have unstable angina or NSTEMI who had medical management.	ASA/CLOP, ASA/prasugrel 10 mg, ASA/prasugrel 5 mg.	Cancer event rate Median follow up 17 months for all cancers, lung cancer, prostate cancer, pancreatic cancer, colorectal cancer and hematologic cancer.
TRITON TIMI 38 trial (11,	RCT; International; 2004-2007.	13,608 (Prasugrel n=6,813, CLOP n=6,795).	Participants had ACS scheduled for PCI.	Prasugrel, CLOP.	Cancer event rate and mortality

20)					Follow up between 6-15 months for all cancers.

ASA=aspirin, CLOP=clopidogrel, RCT=randomized controlled trial.

Table II: Quality assessment of included studies using Cochrane Collaboration Tool for randomised controlled trials and the Newcastle Ottawa Scale for cohort studies.

Randomised Controlled Trials[1]						
Study ID	**Selection Bias**	**Performance Bias**	**Detection Bias**	**Attrition Bias**	**Reporting Bias**	**Overall Quality**
CAPRIE trial (22)	**Low:** computer-driven randomisation and concealed allocation	**Low:** double blind, placebo controlled	**Low**	**Low**: both groups had similar loss to followup of 0.22%	**Low**	**High**
CHARISMA trial (13)	**Unclear:** voice-response system randomisation, but no information on allocation concealment	**Low:** double blind, placebo controlled	**Low**	**Unclear**	**Low**	**Average**
CURE trial (19)	**Low**: computer-driven randomisation and concealed	**Low**: double blind, placebo controlled	**Low**: event adjudication by clinicians blinded to treatment allocation	**Low**: 0.01% loss to follow-up in both groups	**Low**	**High**

	allocation					
DAPT study (12)	**Low**: computer-driven randomisation and concealed allocation	**Low**: double blind, placebo controlled	**Low:** event adjudication by clinicians unaware of treatment assignment	**Low**: 5.7% loss to follow-up in both groups	**Low**	**High**
TRILOGY trial (21)	**Unclear**	**Low**: double blind, active-controlled trial	**Unclear**	**Low**: 0.05% loss to follow-up in both groups	**Low**	**Average**
TRITON TIMI-38 trial (11, 20)	**Low**: random assignment with double dummy medication	**Low**: double blind, active-controlled trial	**Low**: event adjudication by clinicians unaware of treatment assignment	**Unclear**: no info per group but in total 0.1% were lost to follow-up	**Low**	**High**
Cohort Studies[2]						
Study ID	**Selection (max: ****)**		**Comparability (max: **)**	**Outcome (max: ***)**		**Overall Quality**
Leader 2015 (conference abstract) (24)	******* group representative of local population, both cohorts from same community, ascertainment of exposure using prescriptions, unclear if outcome of interest present at the beginning though		****** Multivariate analysis to control for confounding factors	****** Likely record linkage owing to use of ICD-9 coding for outcome adjudication, sufficiently long follow-up of median 155, but no		**Average**

	very unlikely		statement on loss to follow-up	
Lee 2015 (conference abstract) (23)	* Patient group with hepatitis, but comparator group from the same community. no information on whether the outcome of interest was present at the beginning neither on how exposure was ascertained	** Use of a multivariable Cox proportional hazards model	No description on how outcome was ascertained, neither on follow-up period or loss to follow-up.	**Low**
Hicks 2015 (journal paper) (14)	**** UK wide population using GP prescription data from the UK Clinical Practice Research Datalink to ascertain exposure, patients with previous diagnosis at start of study were excluded	** Use of a multivariable time-dependent Cox regression models to adjust for confounders	*** Outcome was ascertained by linkage with the National Cancer Data Repository and UK Clinical Practice Research Datalink	**High**

1: Cochrane Collaboration Tool (16) , 2: Newcastle Ottawa scale (17)

Table III: Study results

Study ID	Results
CAPRIE trial (22)	Lung Cancer: Clopidogrel 75 mg 72/9553 vs aspirin 325 mg 74/9546.
CHARISMA trial (13)	Cancer mortality for clopidogrel/aspirin 75-162 mg vs placebo/aspirin 75-162 mg: aHR: 0.854 (0.588-1.240). Event rate: 51/7,801 vs 60/7,801. Lung cancer for clopidogrel/aspirin aspirin 75-162 mgvs placebo/aspirin 75-162 mg: Event rate 70/7,802 vs 63/7,801.
CURE trial (19)	Colorectal Cancer: Clopidogrel 75 mg/aspirin 75-325 mg 16/6259 vs placebo/aspirin 75-325 mg 8/6303 Lung Cancer: Clopidogrel 75 mg/aspirin 75-325 mg 12/6259 vs placebo/aspirin 75-325 mg 7/6303
DAPT study (12)	Cancer incidence with thienopyridine continuation/aspirin vs placebo/aspirin: enrolment to randomisation 23/5,862 vs 28/5,786. After randomization (12-33 months) 117/5,862 vs 92/5,786. Cancer mortality with thienopyridine continuation/aspirin vs placebo/aspirin: 34/5,862 vs 17/5,786. Cancer location in related deaths with thienopyridine continuation/aspirin vs placebo/aspirin: Lung cancer: 10/5862 vs 9/5786. Prostate cancer: 5/5862 vs 0/5786. Pancreatic: 4/5862 vs 1/5786. Colorectal cancer: 4/5862 vs 0/5786. Hematologic cancer: 2/5862 vs 1/5786.
Hicks 2015 (14)	Colorectal cancer mortality with clopidogrel use: aHR 0.98 (0.77-1.24). Event rate 72/509 vs 2,649/9,850. Breast cancer mortality with clopidogrel use: aHR 1.22 (0.90-1.65). Event rate 46/463 vs 2,172/17,426. Prostate cancer mortality with clopidogrel use: aHR 1.03 (0.82-1.28). Event rate 91/850 vs 1,917/12,305.
Leader 2015 (24)	Cancer with aspirin only: aHR 0.54 (0.52-0.56). Event rate 5,692/64,362 vs 8,816/75,624. Cancer with clopidogrel only: aHR 0.37 (0.23-0.58). Event rate 18/271 vs 8,816/75,624. Cancer with aspirin/clopidogrel: aHR 0.46 (0.44-0.49). Event rate 1,286/15,103 vs 8,816/75,624.
Lee 2015 (23)	Hepatocellular carcinoma and aspirin only: HR 0.18 (0.08-0.39). Hepatocellular carcinoma and clopidogrel only: HR 0.11 (0.02-0.81). Hepatocellular carcinoma and aspirin/clopidogrel: HR 0.37 (0.15-0.92).
TRILOGY trial (21)	Prasugrel 5-10 mg OD/aspirin <100 mg OD vs clopidogrel 75 mg OD/aspirin <100 mg OD: any cancer 82/4554 vs 78/4551 HR 1.04 (0.77-1.42), breast cancer 4/4554 vs 2/4551, colorectal cancer 14/4554 vs 6/4551, lung cancer 11/4554 vs 12/4551, prostate cancer 7/4554 vs 8/4551.
TRITON TIMI-38 trial (11, 20)	New, non-benign neoplasm with prasugrel 10 mg/aspirin 75 mg vs clopidogrel 75 mg/aspirin 75 mg: 94/6741 vs 80/6716. Cancer mortality with prasugrel 10 mg/aspirin 75 mg vs clopidogrel 75 mg/aspirin 75 mg:33/6741 vs 21/6716 (RR 1.57 (0.91-2.71)).

Figure II: Cancer event rate with thienopyridine exposure

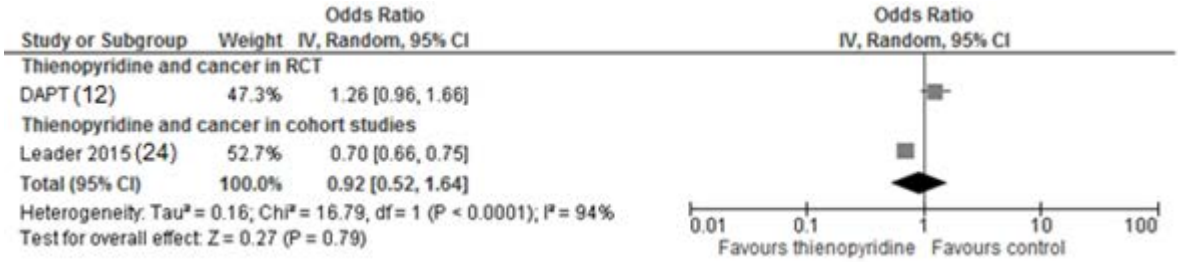

Figure III: Malignancy related mortality and cancer event rate with clopidogrel exposure.

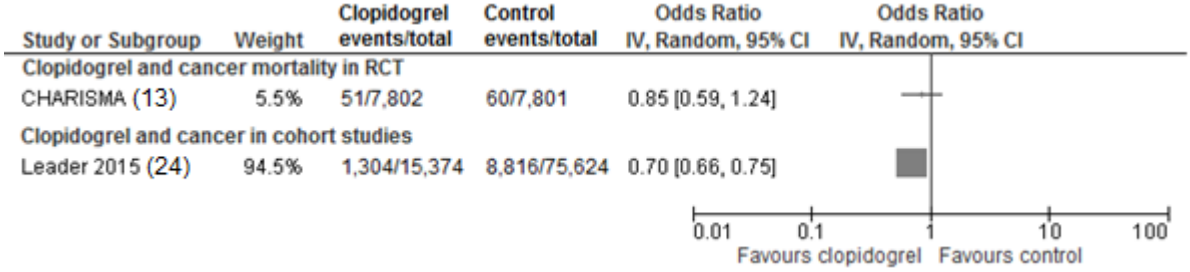

Figure IV: Prasugrel vs clopidogrel in malignancy related mortality and cancer event rate.

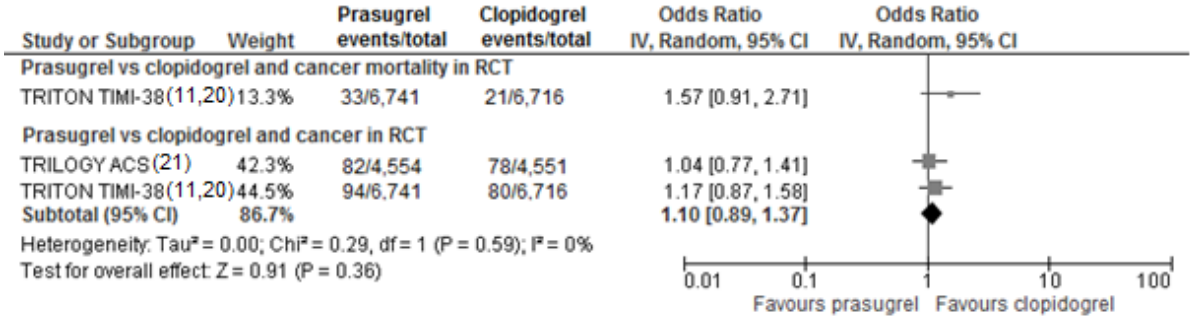

Figure V: Malignancy related mortality with thienopyridine exposure.

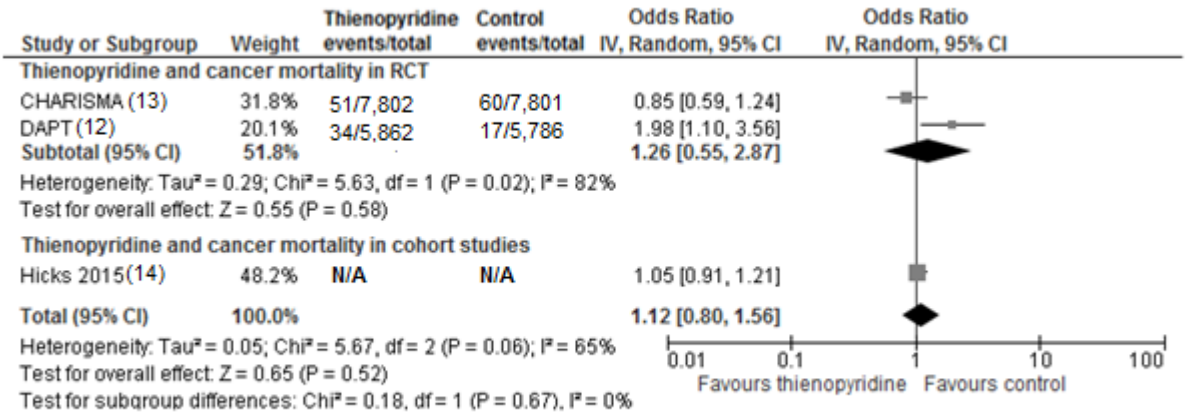

Figure VI: Thienopyridine exposure and cancer event rate by cancer site

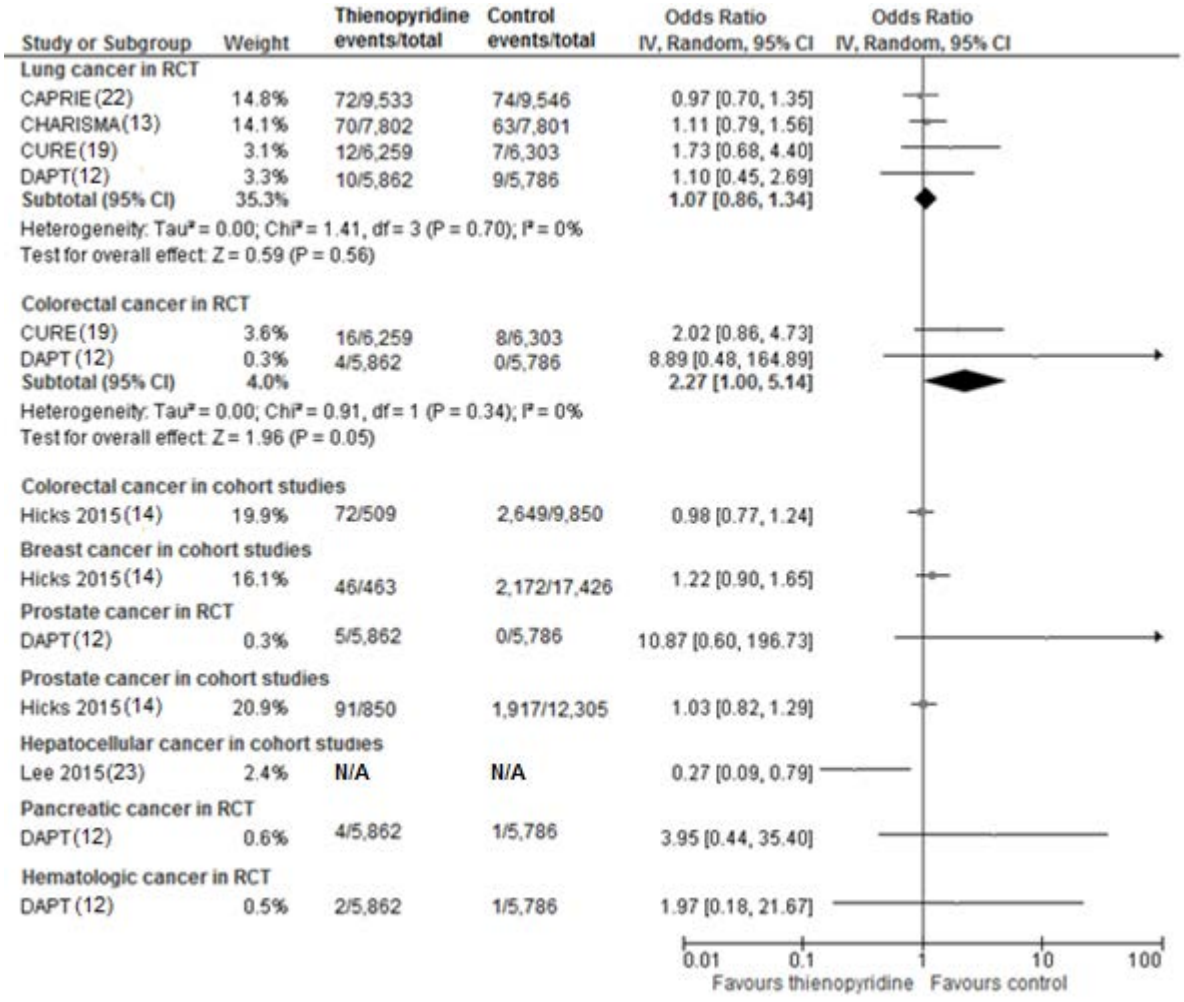

Figure VII: Clopidogrel exposure and cancer event rate by cancer location (excluding prasugrel/ticagrelor)

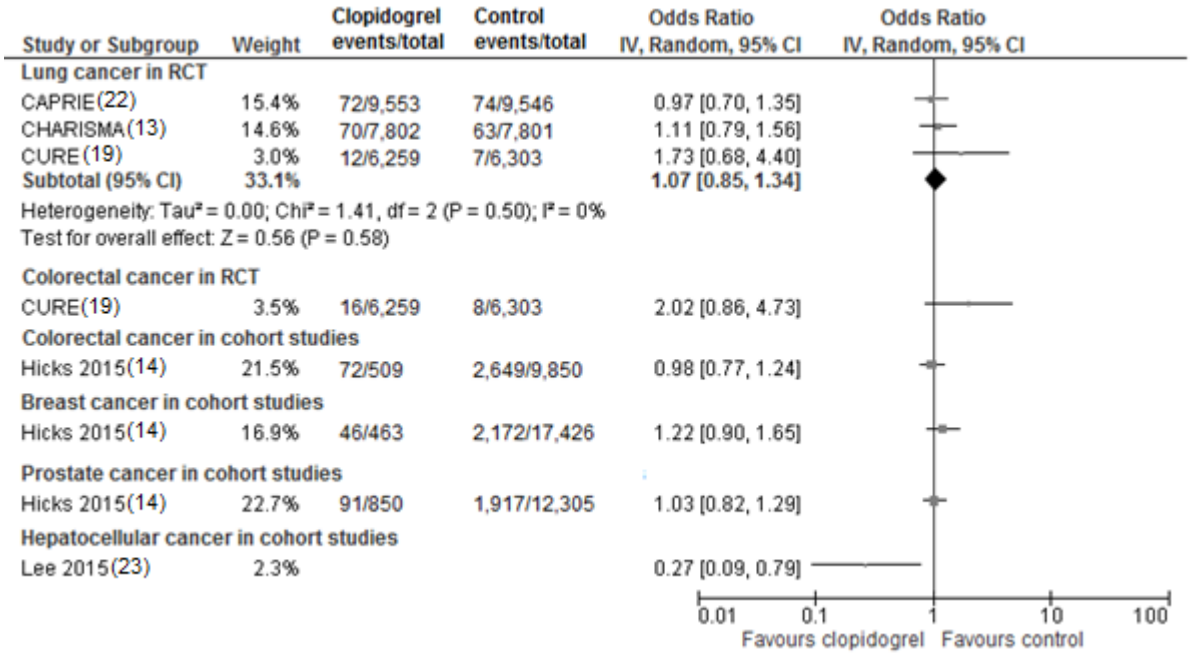

Figure VIII: Prasugrel vs clopidogrel exposure and cancer event rate by cancer location