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Access and non-access site bleeding after percutaneous coronary intervention and risk of subsequent mortality and major adverse cardiovascular events: A systematic review and meta-analysis

Short title: Site-specific bleeding and risk of adverse events

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Abstract

Background: Peri-procedural major bleeding complications following PCI are associated with increased morbidity and mortality outcomes although the influence of site-specific major bleeding complications following PCI on prognostic outcomes has yielded conflicting data. The object of this study is to provide an overview of site-specific major bleeding events in contemporary PCI, and systematically study the association of site-specific major bleeding complications following PCI and mortality and MACE outcomes.

Methods and Results: We conducted a systematic review and meta-analysis of PCI studies that evaluated site-specific peri-procedural bleeding complications and their impact on MACEs and mortality outcomes. A systematic search of MEDLINE and EMBASE was conducted to identify relevant studies and random effects meta-analysis was used to estimate the risk of adverse outcomes with site-specific bleeding complications. 25 relevant studies including 2,400,645 patients that underwent PCI were identified. Both non-access site (RR 4.06 95% CI 3.21-5.14) and access site (RR 1.71 95% CI 1.37-2.13) related bleeding complications were independently associated with an increased risk of peri-procedural mortality. There were differences in the prognostic impact of non-access site related bleeding events on mortality outcomes according to the source of anatomical bleeding, for example gastrointestinal RR 2.78 95% CI 1.25-6.18, retroperitoneal RR 5.87 95% CI 1.63-21.12, intracranial RR 22.71 95% CI 12.53-41.15.

Conclusions: Site-specific bleeding complications following PCI are independently associated with an increased risk of mortality, although the prognostic impact varies according to anatomical source. Non-access site related bleeding complications have a similar prevalence to those derived from the access site but are associated with a significantly worse prognosis.

Introduction

Major bleeding is one of the most common complications following percutaneous coronary intervention (PCI) and is independently associated with a 3-fold increase in mortality and major adverse cardiovascular events (MACE)[1] and contribute up to 12.1% of all in-hospital mortalities following PCI.[2]

There are currently around 10 different definitions of major bleeding used in trials and registries of patients undergoing PCI with these definitions including clinical events, such as blood transfusion or retroperitoneal hemorrhage, laboratory parameters such as decreases in hemoglobin and clinical outcomes such as mortality.[3] Such major bleeding events as defined by different contemporary bleeding definitions have different impacts on mortality outcomes dependent on the definition of major bleeding used that may relate to the different prognostic impact of the different components that make up each individual bleeding definition.[1]

Major bleeding complications occur at several sites such as the arterial access site (in particular the femoral artery), or from non-access site sources such as intracranial, gastrointestinal tract or retro-peritoneum. However, previous studies have reported conflicting data regarding both the prevalence of access and non-access site related bleeding complications[4-7] and their relative prognostic impacts.[4-6, 8-11]

To date there has not been a systematic review or meta-analysis published studying the prevalence or prognostic impact of site-specific bleeding complications following PCI. In this meta-analysis, we provide an overview of the cohorts evaluating the rates of site-specific major bleeding events in studies reporting PCI outcomes, and systematically study the association of site-specific major bleeding complications following PCI and mortality and MACE outcomes.

Methods

Eligibility criteria

We selected studies that studied the impact of site-specific bleeding complications on mortality or major adverse cardiovascular events (MACE) in patients who underwent PCI. Site-specific bleeding complications included: intra-myocardial, pericardial, cardiac tamponade, gastrointestinal, retroperitoneal, intracranial, femoral, access site or non-access site bleeding complications.

Search strategy

A search of EMBASE (1974 to March 2014) and MEDLINE (1946 to March 2014) was conducted on OVID SP. The search terms are shown in Supplemental Table 1. We checked the bibliographies of included studies and relevant review articles found on the search for additional relevant articles.

Study selection and data extraction

Two reviewers (CSK and MAK) checked all titles and abstracts for studies that could potentially meet the inclusion criteria. We retrieved full reports of potentially eligible studies and independently extracted relevant data on study design, participant characteristics, bleeding and outcome events, onto a preformatted spreadsheet. Any discrepancies between the two reviewers were resolved by consensus after consulting another reviewer (MAM or YKL).

Quality assessment

Risk of bias was assessed by considering four different areas: ascertainment of bleeding events, ascertainment of outcome events, extent of loss to follow up and the use of adjustment for confounders in the analysis. We also assess for publication bias using funnel

plots when there were>10 studies available in the meta-analysis and there was no evidence of substantial statistical heterogeneity.[12]

Data analysis

We used RevMan 5.1.7 (Nordic Cochrane Centre) to undertake random effects meta-analysis using the inverse variance methods for pooled risk ratios. We assumed similarity between the risk ratio, and other relative measures such as odds ratio, relative risk, rate ratios or hazard ratios because cardiovascular events and death were rare events.[13] Where there were enough studies, the analysis was stratified based on whether the results had considered the effect of potential confounders through adjustments or propensity matched cohorts or not. In order to reduce the risk of bias from confounders, we appraised studies with multivariate adjustments or propensity matched cohorts separately from studies with crude or unadjusted results. For datasets reporting multiple time-points, we took the earliest time-point for the primary analysis. We performed sensitivity analysis only including randomized controlled trials, considering the effect of anticoagulation and stratifying the analysis of access and non-access site bleeding by indication for PCI. We used the I^2 statistic to assess statistical heterogeneity. I^2 values of 30% to 60% represent moderate levels of heterogeneity. Where there was a high degree of heterogeneity and sufficient number of studies (more than five) in an analysis we performed sensitivity analysis by considering subgroups.

Results

Study selection

The process of study selection is shown in Supplemental Figure 1. We retrieved 25 relevant studies of patients that underwent PCI (total number of subjects 2,400,645), which evaluated the risk of adverse events with and without major bleeding.[2, 4-11, 14-29] Excluded

studies are shown in Supplemental Table 2. The patient cohort size ranged from 73 to 1,216,759 and 106,490 major bleeding events were recorded (23 studies, 4.5%). 22 studies evaluated mortality as an outcome[2, 6, 8-11, 14, 16-21] and 9 studies reported on major adverse cardiovascular events.[5, 7, 14, 15, 19, 23, 25-27]

Description of studies included

Study design, date of study, country of origin and indication for PCI is shown in Table 1. The age and gender of participants along with the anti-platelet and anti-coagulant regimens are shown in Supplemental Table 3. The extent to which femoral access site was used in the include studies is shown in Supplemental Table 4. Supplementary Table 5 illustrates baseline co-variates and procedural demographics that have been adjusted for in each analysis. At total of 13 studies reported the type of access site with a total of 398,903 participants. Among these studies there were 8,097 radial (2%) and 390,806 femoral (98%).

Quality assessment

Supplemental Table 6 shows the quality assessment for included studies. Most studies did not report loss to follow up (n=15)[6, 9-11, 15, 17-20, 22-26, 29] and 10 studies did not adjust for potential confounders.[9, 11, 16-18, 20, 23, 25-27]

Site-specific bleeding and risk of adverse events

Description of the incidence, type and outcomes of major bleeding events are shown in Table 2. Out of the 25 included studies, 7 evaluated access site bleeding complications[2, 4-7, 20, 28] and 6 evaluated non-access site bleeding complications,[2, 4-7, 20] . Other site specific bleeding complications and their associated outcomes are shown in Table 3.

Access and non-access site bleeding

There were 7 studies[2, 4-7, 20, 28] that evaluated adverse outcomes (either mortality or MACE) with access site related bleeding complications (33,677 bleeding events in 301,404 patients, prevalence 11.2%) and 6 studies[2, 4-7, 20] that evaluated non-access bleeding (29,600 bleeding events in 290,456 patients, prevalence 10.2%). Five studies evaluated mortality endpoints[2, 4, 6, 20, 28], the crude mortality rate was 2.8 % (906/31795) in patients who experienced an access site bleed compared to 1.9 % (5001/261676) in the remaining cohort. The crude mortality rate for studies [2, 4, 6, 20] reporting non-access related bleeding complication was 8.3% (2203/26530) vs 1.9% (4923/255140) in the remaining cohort. All studies reported either adjusted estimates or propensity matched cohort data for use in our meta-analysis. The pooled results of 5 studies suggests that the mortality was higher with non-access site bleeding (RR 4.06 95% CI 3.21-5.14, 4 studies) compared to access site bleeding (RR 1.71 95% CI 1.37-2.13, 5 studies) (Figure 1). Only one study reported the risk of MACE[5] with access and non-access site bleeding and the risks were HR 0.74 95% CI 0.16-3.4 and HR 2.66 95% CI 1.21-5.8, respectively. One other study,[7] reported the composite outcome of death and MI and the risk estimate for this composite outcome was not statistically significant for access site bleeding (RR 1.83 95% CI 0.5-6.61) but was significant for non-access site bleeding (RR 2.45 95% CI 1.48-4.04). The pooled risk of adverse outcomes (mortality, mortality and myocardial infarction and MACE) was higher with non-access site bleeding (RR 3.70 95% CI 2.92-4.69, 6 studies) compared to access site bleeding (RR 1.65 95% CI 1.37-1.99, 7 studies) (Supplementary Figure 2). These results are summarized in Table 3. Two studies[8, 27] specifically evaluated the risk of mortality with isolated femoral bleeding complications and there was no significant difference when the results were pooled (RR 2.17 95% CI 0.07-69.22, 2 studies, 103 bleeds, 3,239 no bleeds).

Gastrointestinal bleed

Figure 2 and 3 shows the risk of mortality and MACE considering unadjusted and adjusted results separately. Eight of the ten studies reported crude mortality rate[6, 10, 14, 16-19, 21] which was 13% in patients experiencing a GI bleed (96/738), and 3% in the remaining cohort (1898/55771). There was a significant risk of mortality with GI bleeding which was lower after adjustment (adjusted RR 2.78 95% CI 1.25-6.18 vs unadjusted RR 6.39 95%CI 4.58-8.91) from ten studies[6, 10, 14, 16-19, 21, 22, 29], MACE was considered in 4 studies[14, 19, 21, 23]. The crude rate of MACE with and without GI bleed was 22% (92/417) and 11% (4360/39412) respectively. The risk of MACE was significantly higher in those patients who experienced a GI bleed for the unadjusted studies (RR 2.25 95% CI 1.66-3.05) but not in the adjusted studies (RR 1.23 95% CI 0.55-3.05).

Retroperitoneal, intracranial and femoral bleed

Five studies[6, 8, 9, 11, 26] evaluated 696 retroperitoneal bleeds in 153,489 patients (0.45%) (Table 3). The crude mortality rate in 4 studies [6, 9, 11, 26] was 6.8% in the group who experienced a retroperitoneal bleed (47/696) and 1.6% in the remaining cohort (2377/152793). Retroperitoneal bleeding was associated with a significant increase risk of mortality (RR 5.87 95% CI 1.63-21.12, 5 studies, Figure 4). Two studies[10,28] evaluated the risk of mortality with femoral bleeding and the pooled result showed a trend towards an increase in mortality (OR 2.17 95% CI 0.07-69.22) that was not significant. Intracranial bleeds were evaluated in 1 study[6] that reported 5 deaths in 9 patients who experienced an intracranial bleed and 310 deaths in the remaining 12,670 cohort. The risk ratio for mortality following an intracranial bleed was RR 22.71 95% CI 12.53-41.15.

Intra-myocardial bleed, pericardial bleed and cardiac tamponade

A total of four studies evaluated intramyocardial bleeds, pericardial bleeds and cardiac tamponade.[6, 15, 24, 25](Table 3) Three of the four studies[6, 24, 25] reported crude mortality rates of 8.6% (19/222) in those experiencing a bleed and 2.4% (319/12890) in the remaining group of patients. One study [25] reported the crude rate of MACE of 13.3% (19/143) with intra-myocardial bleeding, compared to 12.1% (21/173) without. There was no significant difference in adverse outcomes (mortality or MACE) with intramyocardial bleeding (RR 1.65 95% CI 0.66-4.13, 2 studies, 154 bleeds, 276 no bleeds) but there were significant increases in mortality with pericardial bleeding (RR 7.71 95% CI 4.37-13.61, 1 study, 53 bleeds, 12,670 no bleed) and cardiac tamponade with coronary perforation (RR 3.30 95% CI 1.02-10.72, 1 study, 26 bleeds, 47 no bleeds). The pooled results of all these studies show that adverse outcomes (mortality or MACE) are increased with intra-myocardial and pericardial bleeding complications (RR 2.96 95% CI 1.07-8.17, 4 studies with 233 bleeds, 12,993 no bleeds) (Figure 5).

Sensitivity analysis only including randomized controlled trials, effect of indication and studies that have adjusted for anti-coagulaton regime.

Sensitivity analysis only including randomized controlled trials is shown in Supplementary Table 7. In general, there were similar estimates for risk of adverse outcomes with access site, non-access site and gastrointestinal bleeding in randomized controlled trials and when all studies were included. Similarly studies that have adjusted for anti-coagulant choice show worse outcomes associated with non-access site bleeds (Supplementary Table 8 and Supplementary Table 9). The effect of indication on access and non-access site bleeding is shown in Supplementary Table 10, Supplementary Figure 3 and Supplementary Figure 4. For access site- bleeding there was a similar bleeding rates across the indications but for non-

access site bleeding there was much higher mortality for STEMI (RR 4.42 95% CI 1.77-11.06) compared to NSTEMI (RR 2.45 95% CI 1.48-4.05).

Discussion

Major bleeding complications are one of the most common complications following PCI and are independently associated with increased risk of morbidity and mortality[1]. The present analysis of 25 studies involving 2,384,458 subjects is the largest to describing the anatomic origin of bleeding after PCI and its prognostic impact. Our analysis suggests that the prognostic impact of bleeding complications on mortality depends on the anatomical source, with relative risks for mortality varying from 1.6-22.7 fold, with the greatest impact on mortality associated with intra-cranial bleeds. Finally, our analysis suggests that non-access site related bleeding complications have a similar prevalence to those derived from the access site (10.2% vs 11.2 %), but are associated with a significantly worse prognosis.

Previous studies have reported conflicting data regarding prognostic impact of access site related bleeding complications, with studies suggesting either no prognostic impact,[5] a prognostic impact in only severe bleeds but not mild to moderate bleeds[7] or associated with increased risk of mortality or cardiovascular events.[2, 4, 6, 7, 20] In contrast, previous studies have consistently shown a relationship between non-access site related bleeding complications and mortality outcomes.[2, 4-7, 20] Our analysis suggests that non-access site related bleeding complications have a significantly greater impact on mortality (RR 4.06 95% CI 3.21-5.14) compared to access site related bleeding complications (RR 1.71 95% CI 1.37-2.13), which is likely to be multi-factorial in origin.

Analysis of the SYNERGY study [7], illustrated that non-access site bleeds accounted for 65% of GUSTO severe bleeds whilst only accounting for 41% of GUSTO mild to moderate bleeding events whilst the majority of access site bleeding complications were

GUSTO mild to moderate bleeds. The prognostic impact of bleeds is related to the severity of the bleeding complication,[1] hence the greater proportion of non-access site bleeds in the GUSTO severe group in this study, may partly explain the greater prognostic impact of non-access site bleeds on outcomes. Similarly in the study of Ndrepepa[6] more severe BARC class 3 and 4 bleeds were more likely to occur from non-access site compared to access site sources.

Systemic bleeding events are more likely to occur in older patients with a greater burden of co-morbid conditions and a more adverse cardiovascular risk profile than in those patients who sustain access site bleeds,[6, 7] and adjustment for the comorbid conditions cannot fully account for unmeasured confounders. Furthermore, the occurrence of non-access site bleeding in patients may not only be a sign of poorer health than in those who sustain an access site related bleed but may also have a greater impact in these patients because of their compromised health at the time of the bleed.

Our analysis suggests that the prevalence of access and non-access site related bleeding complications are similar. Access site related major bleeding complications occur mainly in PCI procedures undertaken through the femoral artery,[30, 31] which has been the major driver for transradial access site adoption as a default access site for PCI in many European and North American centres because of its association with lower mortality[32-34] through a reduction of such access site related major bleeding complications.[30, 34, 35] The magnitude of mortality reduction associated with radial artery access site adoption during PCI appears to be associated with baseline bleeding risk, with the greatest reductions in mortality associated with adoption of the radial access site found in those patients at highest risk from baseline bleeding complications.[34]

Our analysis suggests that whilst the prevalence of access site and non-access site bleeding complications are similar, rapidly evolving practice in interventional cardiology

means that this is likely to change, with recent studies reporting significant changes in access site practice from a national perspective over time with more widespread adoption of radial access in contemporary PCI procedures in both European and North American national registry datasets.[32, 36-38] The development of the radial access site as the predominant access site choice in many countries such as the UK[36] will serve to decrease the prevalence of access site related complications, with non-access site bleeding complications representing the most common bleeding complication. Changes in anti-platelet therapy towards more potent anti-platelet therapies whilst reducing ischemic events may increase the propensity towards major bleeding complications. For example, in the TRITON TIMI-38 trial [39], use of prasugrel was associated with a 30% increase in non-CABG related TIMI major bleeding compared to that seen in the clopidogrel arm whilst in the PLATO trial ticagralor use was associated with a 25% increase non-CABG related TIMI major bleeding.[40] Similarly, anti-coagulant choice is an important determinant of access and non-access site bleeding complications. Changes in anticoagulant practice from heparin and glycoprotein IIb/IIIa regimes to bivalirudin have been demonstrated to be associated with reductions in major bleeding and mortality,[41, 42] with a recent analysis of the NCDR dataset suggesting that changes in anticoagulation strategies over time contributed to approximately 50% of the annual reduction in bleeding observed in ACS and elective PCI[43] with more aggressive anti-coagulant regimes associated with significant increases in bleeding complications observed in many of the studies included in this meta-analysis (Supplementary Table 9)

National datasets have reported significant changes in both access site and non-access bleeding complications over a 5-year period from 2005-2009 in procedures undertaken in different settings. In elective and UA/NSTEMI PCI, reductions in access site bleeding complications have been reported. In contrast, whilst the incidence of non-access site bleeding complications have remained constant in both the elective and NSTEMI setting they

have increased in the STEMI setting.[43] This is likely to represent a complex balance between evolving access site practice and use of pharmacological strategies associated with reduced bleeding risk, offset by changes in patients demographics such increasing patient age and co-morbid conditions, increasingly potent anti-platelet therapy as well as a move from elective PCI to ACS indications over time which serves to increase baseline bleeding risk of the cohorts undergoing PCI procedures.

Our meta-analysis has a number of potential limitations. Firstly, studies included in this meta-analysis have used different definitions of bleeding that will impact both on the reported prevalence of the bleeding complication and it's prognostic impact.[1] Secondly, whilst we have shown that the prognostic impact of non-access site bleeds is greater than that of access site bleeds; it is unclear whether this is driven by the magnitude of the bleeding event. Only 2 studies that have studied the prognostic impact of access vs non access site bleeds have adjusted for either measures of, or surrogates for the magnitude of bleeding[4, 5] (Supplementary Table 5). Verheugt et al[4] adjusted for haemoglobin values amongst other co-variates in their statistical models and showed that access site bleeds were independently associated with 1-year mortality with an adjusted HR of 1.82 (1.17-2.83) and non-access site bleeds with an adjusted HR of 3.94 (3.07-5.15). Similarly, Vranckx et al.[5] adjusted for haemoglobin levels and blood transfusion and demonstrated that the prognostic impact of a non-access site bleed (for the composite endpoint of 12 month Death or AMI) adjusted HR 2.66 (1.21-5.8) was greater than for an access site bleed adjusted HR 0.74 (0.16-3.4). These findings would suggest that even after adjustment for the size of the bleed, non-access site bleeds have a greater impact on prognosis than for access site bleeds. Thirdly, the studies analyzed are a heterogeneous group of studies, containing cohorts of clinical different demographics, undergoing PCI for different indications, treated with different anti-platelet regimens and anti-coagulants and differing access site practice. Whilst we used multivariate-

adjusted or propensity matched risk estimates where available in this analysis, the potential for unmeasured confounders that will impact on outcomes remains. Finally, the majority of the studies analyzed in this current analysis are derived from North American cohorts, where adoption of radial access is still in its infancy outside of a few specialist transradial centers with only around 10% of cases undertaken through the radial artery nationally[44] that may contribute to the high prevalence of access site bleeding complications reported in this analysis.

In conclusion, the present analysis is the most comprehensive review of the varying anatomic origins of bleeding after PCI and their prognostic impact. Our current analysis of 25 studies involving 2,384,458 subjects confirms that site-specific bleeding complications following PCI, irrespective of the anatomical source of bleeding, are independently associated with an increased risk of mortality and that the prognostic impact of bleeding complications on mortality depends on the anatomical source. Finally, our analysis suggests that non-access site related bleeding complications have a similar prevalence to those derived from the access site (10.2% vs 11.2%), but are associated with a significantly worse prognosis. Clinicians should minimize the risk of peri-procedural bleeding complications irrespective of access site adopted during PCI through the use of bleeding avoidance strategies such as the use of anti-coagulants associated with reduced bleeding risk, use of proton pump inhibitors to reduce the risk of GI bleeding complications in those patients at risk, optimal femoral access site practice such as micro-puncture techniques utilizing fluoroscopic or ultrasound guidance for femoral access and utilization of the transradial access site approach for PCI, particularly in patients at high risk of bleeding complications. Particular efforts should be made through careful consideration of pharmacological strategies to reduce non-access site bleeding complications since they have the greatest prognostic impact.

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Table 1: Study design, year of study, country of origin and participant inclusion criteria

Study ID	Design	Date of study	No. of centers	Country	Inclusion criteria
Abbas 2005	Post hoc analysis of randomized controlled trials.	Jun 1990 to Mar 1999.	Multicenter.	International.	Participants had PCI for AMI and were enrolled in the PAMI-1, PAMI-2, NoSOS, Stent-PAMI and Air-PAMI trials.
Amabile 2012	Retrospective cohort study.	Jan 2006 to Oct 2008.	Single center.	France.	Participants had STEMI treated with PCI.
Chhatriwalla 2013	Cohort study.	2004 to 2011	1500 centers.	USA.	Participants had PCI.
Chin 2007	Retrospective case-control study.	Jan 1998 to Jan 2005.	Single center.	Australia.	Participants had PCI for stable angina and acute coronary syndromes.
Chua 2011	Retrospective cohort study.	Jan 2001 to Dec 2006.	Single center.	Taiwan.	Participants had STEMI treated with PCI.
Doyle 2008	Prospective cohort study.	1994 to 2005.	Single center.	USA.	Participants had transfemoral PCI and were included on the Mayo Clinic PCI database.
Ellis 2006	Retrospective cohort study.	1992 to 2003.	Single center.	USA.	Participants had PCI at the Cleveland clinic.
Ergelen 2010	Retrospective cohort study.	Oct 2003 to Mar 2008.	Single center.	Turkey.	Participants had STEMI treated with coronary angiography.
Farouque 2005	Retrospective cohort study.	Jan 2000 to Jan 2004.	Single center.	USA.	Participants had PCI.
Gaglia 2010	Prospectively cohort study.	Jan 2000 to Jan 2010.	Single center.	USA.	Participants had PCI.
Matic 2013	Prospective cohort study.	Aug 2009 to Jan 2011.	Single center.	Serbia.	Participants had STEMI treated with PCI.
Ndrepepa 2013	Post hoc analysis of randomized control trials.	Jun 2000 to May 2011.	Multicenter.	International.	Participants were part of 7 randomized clinical trials (ISAR-REACT, ISAR-SWEET, ISAR-SMART-2, ISAR-REACT-2, ISAR-REACT-3, ISAR-REACT-3A, ISAR-REACT-4).
Nikolsky 2009	Post hoc analysis of randomized control trial.	Aug 2003 to Dec 2005.	450 centers.	International.	Participants were part of ACUITY trial and were randomized to 1 of 3 antithrombotic regimens prior to angiography.
Pres 2010	Retrospective cohort study.	Unclear.	Unclear.	Poland.	Participants with STEMI treated with PCI.
Shivaraju 2011	Retrospective cohort study.	1998 to 2006.	1050 centers.	USA.	Participants were part of National Inpatient Sample with PCI for AMI or CAD diagnoses.
Song 2007	Retrospective cohort study.	Unclear.	Unclear.	China.	Participants had PCI.
Stathoupoulos 2013	Prospective cohort study.	1999 to 2006.	Single center.	USA.	Participants had PCI and coronary perforation.
Thiele 2010	Retrospective cohort study.	Unclear.	Unclear.	Germany.	Participants had STEMI treated with PCI.
Thimarchi 2010	Prospective cohort study.	Oct 2002 to Dec 2007.	Multicenter.	USA.	Participants were in Blue Cross Blue Shield of Michigan Cardiovascular Consortium Registry who had PCI.
Vavalle 2013	Post hoc analysis of randomized controlled trial.	Aug 2001 to Dec 2003.	Multicenter.	International.	Participants were in SYNERGY trial which randomized patients with NSTEMI ACS to enoxaparin or unfractionated heparin.

Verheugt 2011	Post hoc analysis of randomized controlled trial.	Unclear.	Multicenter.	International.	Participants had PCI who were a part of REPLACE-2, ACUITY and HORIZONS-AMI trials.
Vranckx 2012	Post hoc analysis of randomized controlled trial.	Unclear.	16 centers.	Italy, Argentina and Spain.	Participants had STEMI which was treated with PCI and were included in MULTISTRATEGY study.
White 2010	Post hoc analysis of randomized controlled trial.	Recruited Jan 2004 to Dec 2004.	124 centers.	International, 9 countries.	Participants were in STEEPLE trial who were ≥17 years of age and scheduled to undergo elective PCI with a femoral approach.
Yatskar 2007	Cohort study.	Jul 2007 to Mar 2002.	19 centers.	USA.	Participants were in National Heart, Lung and Blood Institute Dynamic Registry who underwent PCI.
Yeh 2013	Cohort study.	2008	1051 centers.	USA.	Participants had acute myocardial infarction who had PCI.

Table 2: Timing of bleeding, definition of major bleeding, follow up

Study ID	Type of bleeding	Time of bleeding	No. in bleeding group	Results
Abbas 2005	GI bleed.	In-hospital.	71	In-hospital: death aOR 3.98 (1.40-11.3) 6 month: death 10/71 vs 139/3039, MACE 15/71 vs 424/3039.
Amabile 2012	Intramyocardial bleed.	In-hospital.	11	Adverse event: aHR 2.8 (1.2-6.8).
Chhatriwalla 2013	Access site and non-access site bleed.	In-hospital.	Access site bleed 30346 2.73%, non-access site 25732 8.25%.	Access site bleed and mortality: 2.73% vs 1.87%, risk difference 0.86% (0.66-1.05%). Non-access site bleed and mortality: 8.25% vs 1.87%, risk difference 6.39% (6.04%-6.73%)).
Chin 2007	GI bleed.	Within 30 days of PCI.	67	Mortality at 30 days: 8 (11.9%) vs 1 (0.5%) and 180 days: 9 (13.4%) vs 1 (0.5%).
Chua 2011	GI bleed.	In-hospital, about one week	18	Crude mortality in-hospital 8/18 bleed vs. 43/501 non-bleed
Doyle 2008	Femoral bleed, retroperitoneal bleed.	Within 30 days.	Femoral bleed/hematoma 855, retroperitoneal 65	Mortality at 30 days: femoral bleed HR 9.96 (6.94-14.3). Mortality at 30 days: retroperitoneal bleed HR 43.8 (16.4-75.1).
Ellis 2006	Retroperitoneal bleed.	In-hospital.	163	Crude mortality: 17/163 (10.4%) vs 198/28215 (0.7%).
Ergelen 2010	GI bleed.	In-hospital.	27	Crude mortality in-hospital: 5/27 (18.5%) vs 73/2514 (2.9%).
Farouque 2005	Retroperitoneal bleed.	In-hospital.	26	Crude mortality in-hospital with retroperitoneal bleed: 1/26 vs 1/50.
Gaglia 2010	GI bleed.	In-hospital.	147	Mortality at 30 days: GI bleed no shock aHR 5.82 (2.56-13.2) and GI bleed shock aHR 10.4 (3.64-29.8), Crude mortality at 1 year: 17.9% vs 4.9%. MACE 1 year aHR 1.23 (0.55-2.79).
Matic 2013	Access site and non-access site bleed.	In-hospital.	Access site bleed: 67, non-access site bleed 51.	Mortality at 1 year access site bleeding vs BARC class 0+1: HR 1.88 (1.01-3.52). Mortality at 1 year non-access site bleeding vs BARC class 0+1: HR 6.80 (3.81-12.14).
Ndrepepa 2013	Access site, non-access site, retroperitoneal, gastrointestinal, pericardial,	30 days.	Access site 905, non-access site 605.	Mortality at 1 year with access site bleeding vs no bleeding: aHR 1.72 (1.19-2.47). Mortality at 1 year with non-access site bleeding vs no bleeding: aHR 2.78 (2.00-3.86). Death with retroperitoneal bleeding: 1/25 vs 310/12,670. Death with gastrointestinal bleeding: 11/152 vs 310/12,670

	intracranial bleed.			Death with pericardial bleeding: 10/53 vs 310/12,670 Death with intracranial bleeding: 5/9 vs 310/12,670
Nikolsky 2009	GI bleed.	30 days. .	178	Mortality at 30 day: crude rate 9.5% vs 1.4%, aHR 4.87 (IQR 2.61-9.08), composite ischemia at 30 day: crude rate 19.8% vs 7.5%, aHR 1.94 (IQR 1.14-3.30). Mortality at 1 year: crude rate 21.9% vs 3.9%, composite ischemia at 1 year: 34.7% vs 16.3%. 1-year all-cause mortality: HR 3.97 (IQR 2.64-5.99).
Pres 2010	GI bleed.	In-hospital.	78	Mortality in-hospital: aOR 1.27 (1.04-1.56). Mortality 3 year: aHR 1.58 (1.07-2.33).
Shivaraju 2011	GI bleed.	In-hospital.	12694	Mortality in-hospital: aOR 4.70 (4.23-5.23).
Song 2007	GI bleed.	In-hospital	21	Crude MACE: 23% vs 9.3%.
Stathoupoulos 2013	Cardiac tamponade.	In-hospital.	26	Mortality in-hospital: 7.7% vs 4.3%. Long term mortality: OR 3.3 (1.01-10.65).
Thiele 2010	Intramyocardial bleed.	In-hospital.	143	Crude MACE: 13% vs 12%. Crude mortality 5% vs 4%.
Thimarchi 2010	Retroperitoneal hematoma.	In-hospital.	482	In-hospital death: 28/482 vs 1868/111858. In-hospital MI: 32/482 vs 1197/111858. In-hospital MACE: 65/482 vs 4676/111858.
Vavalle 2013	Access site and non-access site bleed.	In-hospital.	Access site bleed: 1830. Non-access site bleed: 3070.	Death/MI at 6 months access site bleed: severe HR 3.57 (2.35-5.40), mild/moderate HR 0.96 (0.82-1.2). Death/MI at 6 months: severe surgical bleed HR 5.27 (3.80-7.29), severe systemic bleeds HR 4.48 (2.98-6.72), mild/moderate surgical bleed HR 2.52 (2.16-2.94), mild/moderate systemic bleed HR 1.40 (1.16-1.69), mild/moderate superficial bleed HR 1.17 (0.97-1.40).
Verheugt 2011	Access site and non-access site bleed.	30 days.	Access site 357, non-access site 142	Mortality at 1 year: access site bleed vs no bleed: aHR 1.82 (1.17-2.83). Mortality at 1 year: non-access site bleed vs no bleed: aHR 3.94 (3.07-5.15).
Vranckx 2012	Access site and non-access site bleed.	Within 30 days of PCI	NA	Access site bleed and 12 month death/MI: aHR 0.74 (0.16-3.4). Non access site bleed and 12 month death/MI: aHR 2.66 (1.21-5.8)
White 2010	Femoral hematoma ≥5 cm.	Within 30 days of PCI.	103	Mortality at 1 year: 0/103 vs 55/3229. MACE at 30 days: 6/103 vs 190/3229.
Yatskar 2007	Access site bleeding requiring transfusion.	Unclear.	120	In-hospital mortality: aOR 3.59 (1.66-7.77). 1 year mortality: aOR 1.65 (1.01-2.70).
Yeh 2013	GI bleed.	Mortality.	29010	Mortality: aOR 1.177 (1.111-1.247).

Table 3: Site specific bleeding and risk of morality and major adverse cardiovascular events

Type of bleeding	Studies	Participants with bleed	Participants with no bleed	Risk of adverse outcome
Intramyocardial[15, 25]	2	154	276	MACE: RR 1.65 (0.66-4.13)
Pericardial[6]	1	53	12,670	Mortality: RR 7.71 (4.37-13.61)
Cardiac tamponade with coronary perforation[24]	1	26	47	Mortality: RR 3.30 (1.02-10.72)
Intramyocardial, pericardial or cardiac tamponade [6, 15, 24, 25]	4	233	12,993	Adverse outcomes: RR 2.96 (1.07-8.17)
Gastrointestinal[6, 10, 14, 16-19, 21, 22, 29]	9	42,442	1,875,483	Mortality: Unadjusted: RR 6.39 (4.58-8.91) Adjusted: RR 2.78 (1.25-6.18)
Gastrointestinal[14, 19, 21, 23]	4	417	39,432	MACE: Unadjusted RR: 2.25 (1.66-3.05) Adjusted RR: 1.23 (0.55-3.05)
Retroperitoneal[6, 8, 9, 11, 26]	5	696	152,793	Mortality: RR 5.87 (1.63-21.12)
Intracranial[6]	1	9	12,670	Mortality: RR 22.71 (12.53-41.15)
Femoral[8, 27]	2	103	3,239	Mortality: RR 2.17 (0.07-69.22)
Access site [2, 4-7, 20, 28]	5 7	31,795 33,677	261,676 267,446	Mortality: RR 1.71 (1.37-2.13) Adverse outcomes: RR 1.65 (1.37-1.99)
Non-access site[2, 4-7, 20]	4 6	26,530 29,652	255,140 261,548	Mortality: RR 4.06 (3.21-5.14) Adverse outcomes: RR 3.70 (2.92-4.69)

Figures legends

Figure 1: Risk of mortality with access and non-access site bleeding

Figure 2: Risk of mortality with GI bleed

Figure 3: Risk of MACE with GI bleed

Figure 4: Risk of mortality with retroperitoneal bleed

Figure 5: Risk of adverse outcome with intramyocardial bleed, pericardial bleed or cardiac tamponade

Figure 1: Risk of mortality with access and non-access site bleeding

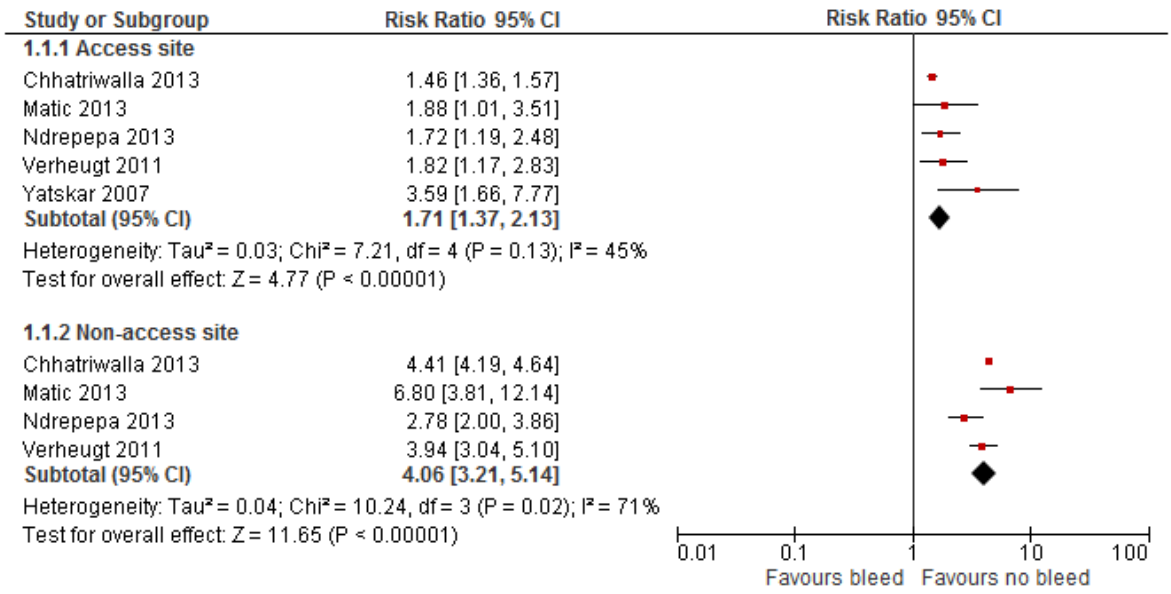

Figure 2: Risk of mortality with GI bleed

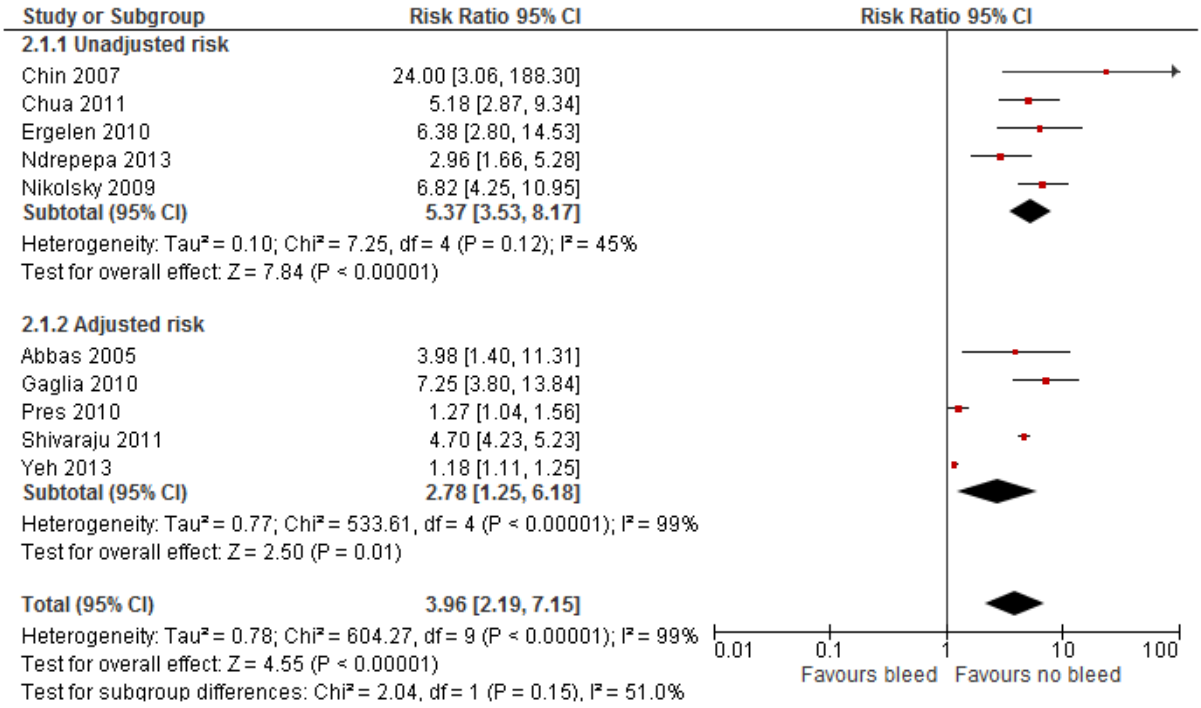

Figure 3: Risk of MACE with GI bleed

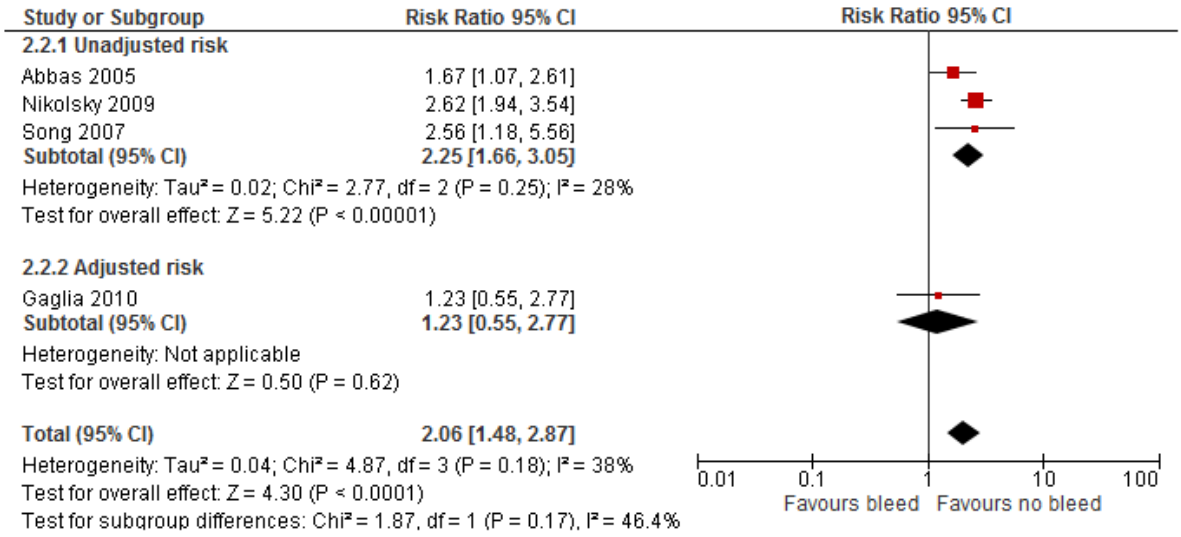

Figure 4: Risk of mortality with retroperitoneal bleed

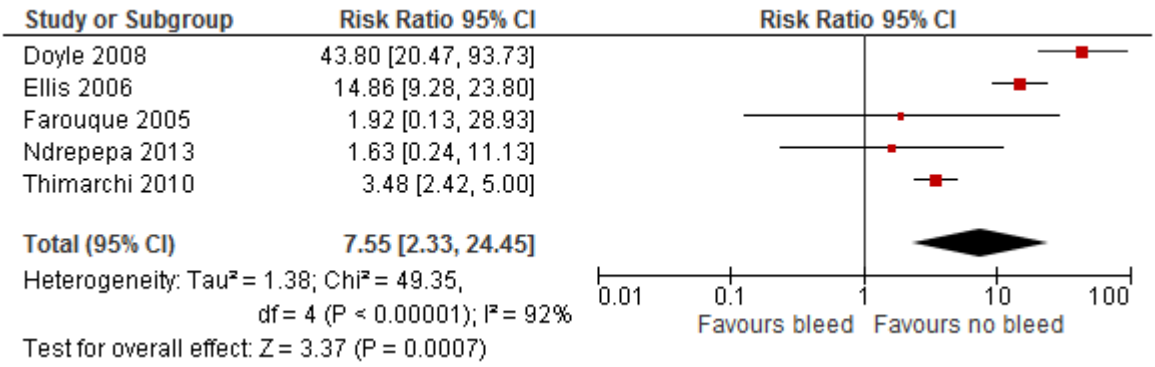
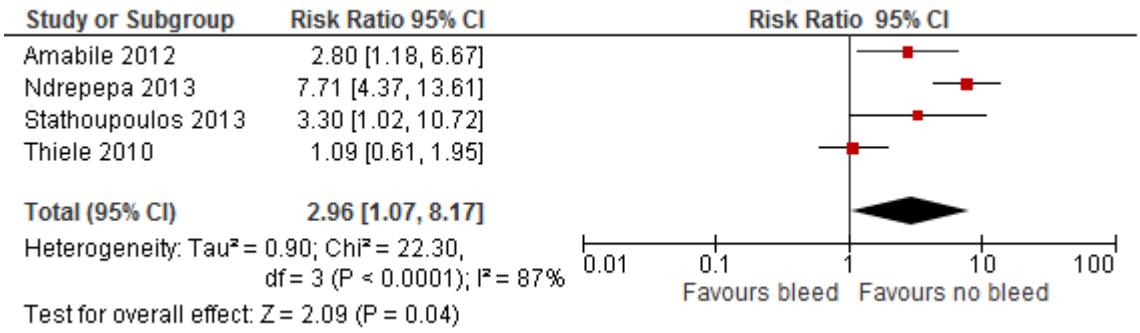
Figure 5: Risk of adverse outcome with intramyocardial bleed, pericardial bleed or cardiac tamponade