A systematic review and economic evaluation of prasugrel compared to clopidogrel after PCI

Report from Kunnskapssenteret (Norwegian Knowledge Centre for the Health Services)
No 5–2011
Health Technology Assessment (HTA) (Medisinsk metodevurdering)

kunnskapssenteret
Norwegian Knowledge Centre for the Health Services

Background: Patients who have undergone percutaneous coronary intervention (PCI) for coronary artery disease usually get a platelet inhibitor (e.g. clopidogrel) for one year after the procedure. Prasugrel is a new platelet inhibitor which is available for patients with acute coronary syndrome (ACS) who undergo PCI in Norway. **Methods:** We aimed to analyze the efficacy and cost-effectiveness of prasugrel compared to clopidogrel for ACS patients who have undergone PCI. This analysis was commis-sioned by the Norwegian Medicines Agency to support their decision on whether to give reimbursement to prasugrel as well as clopidogrel, which is reimbursed today. • We performed a systematic review of randomised controlled trials (RCTs) to estimate the efficacy of prasugrel compared to clopidogrel. Cost-effectiveness analyses were performed in a previously developed Markov model (MOCCA) which simulates clinical events after a PCI is performed. In the model, health and costs are calculated to give the remaining life expectancy and lifetime costs, which again are used to calculate incremental cost-effectiveness of prasugrel compared to clopidogrel. **Key messages:** *(continued)*

Norwegian Knowledge Centre for the Health Services (Kunnskapssenteret)
PO Box 7004, St. Olavs plass
N-0130 Oslo
(+47) 23 25 50 00
www.kunnskapssenteret.no
Report: ISBN 978-82-8121-401-9 ISSN 1890-1298

no 5–2011

kunnskapssenteret

(continued from page one) • Prasugrel significantly reduces rates of myocardial infarction and urgent target vessel revascularization compared to clopidogrel in both short term (up to 1 month) and long term (up to 15 months). Quality of the evidence was high and moderate for myocardial infarction and low and moderate for urgent target vessel revascularization. • Prasugrel significantly increases rates of bleeding events compared to clopidogrel in both short term and long term data. Quality of the evidence for this outcome was high and low, respectively. • The analyses on short and long term effects on mortality revealed no statistically significant differences. Quality of the evidence for this outcome was low and moderate, respectively. • Prasugrel is cost-effective compared to clopidogrel for ACS patients who have undergone PCI. Our analyses indicate however that there is uncertainty surrounding the cost-effectiveness result. • Uncertainty related to efficacy on mortality and, hence also, cost-effectiveness could be reduced if new randomised controlled trials are performed.

Title	A systematic review and economic evaluation of prasugrel compared to clopidogrel after PCI
Norwegian title	En kunnskapsoppsummering og helseøkonomisk evaluering av prasugrel sammenlignet med klopidogrel etter PCI
Institution	Nasjonalt kunnskapssenter for helsetjenesten (Norwegian Knowledge Centre for the Health Services)
Authors	Wisløff, Torbjørn, *senior adviser* Tove Ringerike, *senior researcher* Marianne Klemp, *research director*
ISBN	978-82-8121-401-9
ISSN	1890-1298
Report	Nr 5 – 2011
Project number	581
Type of report	Health Technology Assessment (Medisinsk metodevurdering)
No. of pages	42 (53 appendices included)
Client	Norwegian Medicines Agency
Keywords	Kunnskapssenteret, kunnskapsenter, prasugrel, clopidogrel, coronary artery disease, myocardial infarction, angina pectoris, cost-effectiveness, economic evaluation, pharmaceuticals, pharmacoeconomics.
Citation	Wisløff T, Ringerike T, Klemp M. Economic evaluation of prasugrel compared to clopidogrel after PCI. Report nr 5-2011. Oslo: Norwegian Knowledge Centre for the Health Services, 2011.

Norwegian Knowledge Centre for the Health Services summarizes and disseminates evidence concerning the effect of treatments, methods, and interventions in health services, in addition to monitoring health service quality. Our goal is to support good decision making in order to provide patients in Norway with the best possible care. The Centre is organized under The Norwegaian Directorate of Health, but is scientifically and professionally independent. The Centre has no authority to develop health policy or responsibility to implement policies.

We would like to thank Lars Granum, Inger Natvig Norderhaug, Vida Hamidi, Bjarne Robberstad, Sigrun Halvorsen, Eamonn Noonan, Gunn Elisabeth Vist, Ingrid Harboe and Gunhild Hagen for their expertise and helpful insights in this project. Norwegian Knowledge Centre for the Health Services assumes final responsibility for the content of this report.

Norwegian Knowledge Centre for the Health Services
Oslo, April 2011

Key messages

A systematic review and economic evaluation of prasugrel compared to clopidogrel after PCI

Patients who have undergone percutaneous coronary intervention (PCI) for coronary artery disease usually get a platelet inhibitor (e.g. clopidogrel) for one year after the procedure. Prasugrel is a new platelet inhibitor which is available for patients with acute coronary syndrome (ACS) who undergo PCI in Norway.

We aimed to analyze the efficacy and cost-effectiveness of prasugrel compared to clopidogrel for ACS patients who have undergone PCI. This analysis was commissioned by the Norwegian Medicines Agency to support their decision on whether to give reimbursement to prasugrel as well as clopidogrel, which is reimbursed today. We performed a systematic review of randomised controlled trials (RCTs) to estimate the efficacy of prasugrel compared to clopidogrel. Cost-effectiveness analyses were performed in a previously developed Markov model (MOCCA) which simulates clinical events after a PCI is performed. In the model, health and costs are calculated to give the remaining life expectancy and lifetime costs, which again are used to calculate incremental cost-effectiveness of prasugrel compared to clopidogrel.

Key messages

- Prasugrel significantly reduces rates of myocardial infarction and urgent target vessel revascularization compared to clopidogrel in both short term (up to 1 month) and long term (up to 15 months). Quality of the evidence was high and moderate for myocardial infarction and low and moderate for urgent target vessel revascularization.
- Prasugrel significantly increases rates of bleeding events compared to clopidogrel in both short term and long term data. Quality of the evidence for this outcome was high and low, respectively.
- The analyses on short and long term effects on mortality revealed no statistically significant differences. Quality of the evidence for this outcome was low and moderate, respectively.
- Prasugrel is cost-effective compared to clopidogrel for ACS patients who have undergone PCI. Our analyses indicate however that there is uncertainty surrounding the cost-effectiveness result.
- Uncertainty related to efficacy on mortality and, hence also, cost-effectiveness could be reduced if new randomised controlled trials are performed.

Executive summary

BACKGROUND

Patients who have undergone percutaneous coronary intervention (PCI) for acute coronary syndrome (ACS) usually get a platelet inhibitor (clopidogrel) for one year after operation. Prasugrel is a new platelet inhibitor which is available for ACS patients who undergo PCI in Norway.

OBJECTIVE

To analyse the cost-effectiveness of prasugrel compared to clopidogrel for ACS patients who have undergone PCI.

METHODS

We searched Medline and Embase for randomised controlled trials (RCTs) on efficacy of prasugrel compared to clopidogrel on 08.02.2010 and 15.03.2011. Trials were assessed by two independent reviewers and combined into meta-analyses on the outcomes cardiovascular death, acute myocardial infarction (AMI), urgent target vessel revascularization (UTVR) and bleeding events. The quality of the evidence was evaluated using GRADE (Grading of Recommendations, Assessment, Development and Evaluation).

We used a modified version of a Markov model (Model of cost-effectiveness of coronary artery disease (MOCCA)) previously developed by Norwegian Knowledge Centre for the Health Services, to model the cost-effectiveness of prasugrel compared to clopidogrel. Possible events in the model were UTVR, myocardial infarction, bleeding and death. Incidences of events were based on registries from Sweden and Denmark. Costs of prasugrel and clopidogrel were based on list prices from the Norwegian Medicines Agency.

In addition, we performed probabilistic sensitivity analyses, designed as a Monte Carlo simulation with 1 000 iterations, to get an impression of the uncertainty surrounding our analyses.

RESULTS

We found three relevant trials with 14624 participants comparing prasugrel with clopidogrel. All three reported short-term outcomes (14-30 days) and one trial reported also long-term follow-up (15 months). Meta-analyses of short-term outcomes showed that prasugrel significantly lowered need for UTVR, relative risk (RR)=0,53 (95% confidence interval: 0,39-0,73) and AMI, RR=0,75 (0,65-0,86) compared to clopidogrel. However, prasugrel led to increased rates of bleeding (RR=1,24 (1,00-1,53)). Quality of the evidence for these three outcomes were regarded to be low, high and high, respectively.

On long term, prasugrel also had lower rates of UTVR and AMI at RR=0,67 (0,55-0,82) and RR=0,76 (0,68-0,86), respectively. As in short term, bleeding rates were also higher for prasugrel than clopidogrel RR=1,31 (1,10-1,55). These three outcomes were graded to be at moderate, moderate and low quality of evidence, respectively.

The meta-analyses failed to show any differences in mortality between the two drug regimens (short term: RR=0,79 (0,57-1,10), long term: RR=0,88 (0,70-1,11)). Quality of the evidence on mortality was rated to be of low and moderate quality, respectively.

Our modelling resulted in an increase in both life expectancy and costs with prasugrel. This gave an incremental cost-effectiveness ratio of NOK 37 600 per life year gained for prasugrel compared with clopidogrel. The probabilistic sensitivity analyses demonstrated that prasugrel is cost-effective in 88% of the simulations. From our value of information analysis, it became evident that the decision depends mostly on the uncertainty in data on efficacy, and hence if new research should be conducted, this is the kind of data that has the highest potential to reduce the decision uncertainty.

DISCUSSION

Efficacy data on the comparison of prasugrel and clopidogrel was scarce. Based on GRADE, only short term efficacy data on myocardial infarction and bleeding had high quality. Hence, this comparison would benefit from further research.

The incremental cost-effectiveness ratio of NOK 37 600 per life year gained, indicates that prasugrel is clearly cost-effective compared to clopidogrel if a threshold for cost-effectiveness is in the range of 350 000 to 1 000 000. Simulations indicated, however, that this result is uncertain. Further research on the efficacy and safety of prasugrel compared to clopidogrel is particularly likely to reduce uncertainty in conclusions of this analysis.

CONCLUSION

Prasugrel is likely to be more cost-effective than clopidogrel for ACS patients who have undergone PCI. This conclusion is, however, uncertain, and even for high levels of willingness to pay for health, there is a probability of clopidogrel being cost-effective.

Norwegian Knowledge Centre for the Health Services
PB 7004 St. Olavs plass
N-0130 Oslo, Norway
Telephone: +47 23 25 50 00
E-mail: post@kunnskapssenteret.no
Full report (pdf): www.kunnskapssenteret.no

Hovedfunn (norsk)

En kunnskapsoppsummering og økonomisk evaluering av prasugrel sammenlignet med klopidogrel etter PCI

Pasienter som har gjennomgått perkutan koronar intervensjon (PCI) for koronarsykdom vil vanligvis få blodplatehemmer (f.eks. klopidogrel) i ett år etter inngrepet. Prasugrel er en ny platehemmer som er tilgjengelig for pasienter med akutt koronarsyndrom som gjennomgår PCI i Norge.

Vi ønsket å analysere effekten og kostnadseffektiviteten av prasugrel sammenlignet med klopidogrel for pasienter med akutt koronarsyndrom som har gjennomgått PCI. Denne analysen er bestilt av Statens legemiddelverk for å støtte deres beslutning om hvorvidt det skal gis refusjon til prasugrel i tillegg til klopidogrel, som har refusjon i dag. Vi utførte en systematisk gjennomgang av randomiserte kontrollerte studier for å beregne effekten av prasugrel sammenlignet med klopidogrel. Kostnadseffektivitetsanalysene ble utført i en tidligere utviklet Markov-modell som simulerer kliniske hendelser etter utført PCI. I modellen er helseeffekter og kostnader beregnet for å gi gjenstående levealder og levetidskostnader, som igjen brukes til å beregne forholdet mellom kostnader og helseeffekter av prasugrel sammenlignet med klopidogrel.

Hovedfunn

• Prasugrel reduserer forekomsten av hjerteinfarkt og revaskularisering sammenlignet med klopidogrel både på kort og lang sikt (14-30 dager og 15 måneder). Kvaliteten på dokumentasjonen var høy og moderat for hjerteinfarkt og lav og moderat for revaskularisering (på henholdsvis kort og lang sikt).
• Prasugrel øker forekomst av blødninger sammenlignet med klopidogrel både i korttids- og langtidsdata. Kvaliteten på dokumentasjonen for dette utfallet var henholdsvis høy og lav.
• Analysene viste ingen statistisk signifikante forskjeller på død. Kvaliteten på dokumentasjonen for dette utfallet var lav og moderat for henholdsvis korttids- og langtidsdata.
• Prasugrel synes å være kostnadseffektivt sammenlignet med klopidogrel for pasienter med akutt koronarsyndrom som har gjennomgått PCI. Våre analyser antyder imidlertid at det er noe usikkerhet knyttet til resultatet.
• Usikkerhet knyttet til effekt på død, og dermed også kostnadseffektiviteten av prasugrel, kan reduseres dersom nye randomiserte kontrollerte studier blir utført.

Sammendrag (norsk)

BAKGRUNN

Pasienter som har gjennomgått perkutan koronar intervensjon (PCI) for akutt koronarsyndrom vil vanligvis få platehemmer (klopidogrel) i ett år etter operasjonen. Prasugrel er en ny platehemmer som er tilgjengelig for pasienter med akutt koronarsyndrom som gjennomgår PCI i Norge.

FORMÅL

Å analysere kostnadseffektiviteten av prasugrel sammenlignet med klopidogrel for pasienter med akutt koronarsyndrom som har gjennomgått PCI.

METODE

Vi søkte Medline og Embase etter randomiserte kontrollerte forsøk på effekt av prasugrel sammenlignet med klopidogrel den 8.2.2010 og 15.3.2011. Studier ble vurdert av to uavhengige medarbeidere og samlet i meta-analyser på utfallene kardiovaskulær død, akutt hjerteinfarkt, revaskularisering og blødninger. Kvaliteten på dokumentasjonen ble evaluert ved hjelp av GRADE (Grading of Recommendations, Assessment, Development and Evaluation).

Vi brukte en modifisert versjon av en Markov-modell (Model of cost-effectiveness of coronary artery disease (MOCCA)), tidligere utarbeidet av Kunnskapssenteret, til å modellere kostnadseffektiviteten av prasugrel sammenlignet med klopidogrel. Mulige hendelser i modellen var revaskularisering, hjerteinfarkt, blødning og død. Forekomst av hendelser var basert på registerdata fra Sverige og Danmark. Priser på prasugrel og klopidogrel var basert på listepriser fra Statens legemiddelverk. Disse viser at prasugrel er betydelig dyrere enn klopidogrel.

Analysene ble utført ved at all usikkerhet i modellen var representert ved sannsynlighetsfordelinger. Resultatene i modellen er derfor basert på 1 000 tilfeldige trekninger fra disse fordelingene.

RESULTAT

Vi fant tre aktuelle studier (med til sammen 14624 pasienter) som sammenligner prasugrel med klopidogrel. Alle tre rapporterte kortsiktige resultater (14-30 dager), en studie rapporterte i tillegg lang oppfølging (15 måneder). Meta-analyser av resultater med kort oppfølging viste at prasugrel betydelig senket behov for revaskularisering, relativ risiko (RR) = 0,53 (95 % konfidensintervall: 0,39-0,73) og akutt hjerteinfarkt, RR = 0, 75 (0,65-0,86) sammenlignet med klopidogrel. Prasugrel førte imidlertid også til økt forekomst av blødninger (RR = 1,24 (1,00-1,53)). Dokumentasjonskvaliteten for disse tre utfallene ble ansett å være henholdsvis lav, høy og høy.

Prasugrel hadde også lavere langtids forekomst av revaskularisering og akutt hjerteinfarkt på henholdsvis RR = 0,67 (0,55-0,82) og RR = 0,76 (0,68-0,86). Som med kort oppfølging, var forekomsten av blødninger på lang sikt også høyere for prasugrel enn klopidogrel RR = 1,31 (1,10-1,55). Dokumentasjonen for disse tre utfallene ble gradert til henholdsvis moderat, moderat og lav kvalitet.

Meta-analyser klarte ikke å vise eventuelle forskjeller i dødelighet mellom de to medikamentregimene (kort sikt: RR = 0,79 (0,57-1,10), lang sikt: RR = 0,88 (0,70-1,11)). Dokumentasjonskvaliteten på dette utfallet ble vurdert å være av lav og moderat kvalitet med henholdsvis kort og lang oppfølging.

Vår modellering resulterte i økning av både forventet gjenstående levetid og livstidskostnader med prasugrel. Kostnadseffektiviteten av å bytte fra klopidogrel til prasugrel ble dermed på 37 600 norske kroner per vunnet leveår. Sensitivitetsanalysen viste at det er 88 % sannsynlighet for at prasugrel er kostnadseffektiv sammenlignet med klopidogrel. Fra vår verdi av forskningsanalyse, ble det klart at resultatet avhenger mest av effektdataene. Hvis ny forskning skal gjennomføres, er det derfor kliniske studier som undersøker effekt av prasugrel som mest sannsynlig vil redusere usikkerheten rundt resultatet.

DISKUSJON

Vi fant lite effektdata på sammenligning av prasugrel og klopidogrel. Basert på GRADE, hadde bare korttids effektdata på hjerteinfarkt og blødninger høy kvalitet. Derfor vil denne sammenligningen ha nytte av videre forskning.

Kostnadseffektiviteten på 37 600 norske kroner per vunnet leveår, indikerer at prasugrel er klart kostnadseffektivt sammenlignet med klopidogrel dersom en terskel for kostnadseffektivitet er i størrelsesorden 350 000 til 1 000 000. Simuleringer indikerte imidlertid at dette resultatet er usikkert. Videre forskning på effekt og sikkerhet av prasugrel sammenlignet med klopidogrel er forventet å redusere usikkerheten i konklusjonene i denne analysen.

KONKLUSJON

Prasugrel synes å være kostnadseffektivt sammenlignet med klopidogrel for pasienter med akutt koronarsyndrom som har gjennomgått PCI. Våre analyser antyder imidlertid at det er noe usikkerhet knyttet til resultatet.

Glossary and abbreviations

CI	**Confidence interval.** A measure of uncertainty around the results of a statistical analysis that describes the range of values within which we can be reasonably sure that the true mean effect lies. Wider intervals indicate lower precision; narrow intervals, greater precision.
ICER	**Incremental cost-effectiveness ratio**. The ratio of the difference in costs between two alternative health technologies divided by the difference in effectiveness between the same two technologies. $ICER = \frac{Cost_{\text{intervention}} - Cost_{\text{comparator}}}{Effect_{\text{intervention}} - Effect_{\text{comparator}}} = \frac{\Delta C}{\Delta E}$
Meta-analysis	Statistical method to combine results from different studies with similar properties
Monte Carlo simulation	**Monte Carlo simulation** is drawing random numbers from predefined distributions.
PSA	**Probabilistic sensitivity analysis.** An analysis of the uncertainty related to all parameters in a decision analytic model. Typically performed by Monte Carlo simulation, hence by drawing values from probability distributions for all parameters simultaneously
RCT	**Randomised controlled trial.** An experiment in which investigators use randomisation to allocate participants into treatment arms that are being compared. Usually allocation is made at the level of individuals, but sometimes it is done at group level e.g. by schools or clinics. This design allows assessment of the relative effects of interventions.
RR	**Relative risk / risk ratio.** The relative risk is the absolute risk (AR) in the intervention group divided by the AR in the control group. It is to be distinguished from odds ratio (OR) which is the ratio of events over non-events in the intervention group over the ratio of events over non-events in the control group.
SR	**Systematic review.** A review in which specified and appropriate methods have been used to identify, appraise, and summarise studies address-

	ing a defined question. It can, but need not, involve meta-analysis.
Statistically significant	Means that the findings of a study are unlikely to have arisen because of chance. Significance at the commonly cited 5% level ($P < 0.05$) means that the observed difference or greater difference would occur by chance in only 5 out of 100 similar cases. Where the word "significant" or "significance" is used without qualification in the text, it is being used in this statistical sense.
WTP (λ)	**Willingness to pay**. A pre-specified limit of what society is willing to pay for a given health unit (e.g. QALY or life year). In Norway it is common to use NOK 500 000 per QALY or life year in economic evaluations. Sometimes also called cost-effectiveness threshold.

Table of contents

Preface

In the summer of 2009, the Norwegian Knowledge Centre for the Health Services (NOKC) was contacted by the Norwegian Medicines Agency (NoMA) regarding a comparison of prasugrel (Efient) and clopidogrel (Plavix). The aim of the request was to consider possibilities of comparing the cost-effectiveness of a newer drug (prasugrel) with the currently most used drug (clopidogrel) for patients with acute coronary syndrome (ACS) who have recently undergone a percutaneous coronary intervention (PCI). In October 2009 NOKC received a formal order of this project. The commission was to use a previously developed model (1) to evaluate the comparative cost-effectiveness of the drugs in a Norwegian setting.

The project was executed by senior adviser Torbjørn Wisløff (NOKC) and senior researcher Tove Ringerike (NOKC). Lars Granum from NoMA provided guidance and helpful input. Tove Ringerike has been responsible for the systematic review of efficacy, while Torbjørn Wisløff has been responsible for the economic evaluation. Research director Marianne Klemp had the overall supervision of the project. Parts of the methods chapter and glossary are based on NOKC's template for HTA reports.

The aim of this report is to support well-informed decisions regarding follow up of ACS patients who have recently undergone PCI. Results should be considered in accordance with other relevant factors, such as clinical experience and patient preferences.

Gro Jamtvedt	Marianne Klemp	Torbjørn Wisløff
Department director	*Research director*	*Senior adviser, project leader*

Objective

The objective of this report is to evaluate whether prasugrel is effective and cost-effective compared to clopidogrel for patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI). The analysis is conducted to support decisions regarding use and reimbursement of prasugrel.

Background

The Norwegian Medicines Agency (NoMA) received an application for reimbursement of prasugrel (Efient) for patients with acute coronary syndrome (ACS) who undergo PCI. The application was based on a cost-effectiveness analysis presented by the manufacturer and based on old data from countries outside Scandinavia, and there was great uncertainty regarding the validity of the results in a Norwegian setting. NoMA wanted us to use one of our more recent models on cardiovascular prevention to evaluate the cost-effectiveness for this new drug (prasugrel) compared to the older clopidogrel (1).

Evidence indicates that prasugrel has better efficacy on cardiovascular outcomes compared to clopidogrel, but at the same time it is associated with an increased risk of bleeding (2). Hence, a model for cost-effectiveness would have to incorporate both the efficacy and safety perspectives to enable a balanced decision.

ACUTE CORONARY SYNDROME (ACS)

ACS is a term often used to describe patients who have either acute myocardial infarction (AMI) or unstable angina pectoris (UAP). ACS is hence a subgroup of coronary artery disease (CAD), which also includes stable angina pectoris. ACS patients are usually treated with PCI, while stable patients can be treated either pharmaceutically or with PCI.

INTRODUCTION TO SYSTEMATIC REVIEWS OF CLINICAL EFFECTIVENESS

Systematic reviews of clinical effectiveness are products of a comprehensive process, including: literature search, study selection, risk of bias evaluations, data extraction, combining findings and quality of evidence evaluations.

Based on predefined research questions, one can develop a search strategy to identify relevant publications in electronic databases for medical research. In addition, the literature search may include reviews of reference lists, contacting field experts and searching for unpublished studies. The aim is to identify all relevant literature

and include studies based on predefined inclusion criteria, specifying relevant populations, interventions, comparisons, outcomes and study design. To reduce bias, two reviewers assess abstracts and potentially relevant full text publications independently for inclusion. The two reviewers also control the data extraction from included studies.

It is common in systematic reviews to evaluate the included studies for risk of bias or quality. This information may be used in addition to considerations of similarity in participants, interventions, comparisons and outcomes in the decision as to whether effect estimates from several trials can be combined statistically in a meta-analysis. The risk of bias or quality should be used along the effect estimates when a conclusion is made in a systematic review.

INTRODUCTION TO ECONOMIC EVALUATIONS OF HEALTH CARE PROGRAMMES

The basic task of any economic evaluation is to identify, measure, value and compare incremental costs and consequences of the alternatives being considered which means that the difference in cost is compared with the differences in consequences (3). Hence, results of economic evaluations can be expressed as an incremental cost-effectiveness ratio (ICER), which is defined by the following equation:

$$ICER = \frac{Cost_{\text{intervention}} - Cost_{\text{comparator}}}{Effect_{\text{intervention}} - Effect_{\text{comparator}}} = \frac{\Delta C}{\Delta E}$$

If the incremental costs are negative and the incremental effects are positive, an intervention is said to be *dominant*. Likewise, positive incremental costs and negative incremental effects, results in interventions being *dominated*. In both these circumstances, the ICER is negative and the economic evaluation has a simple conclusion. Otherwise, the ICER is positive and things are a bit more complicated. The health care sector and society in general is restricted by scarce resources, and economic evaluations are tools to prioritize and maximize benefits within limited budgets. For an economic evaluation to be meaningful in a decision making process, the positive ICER must be judged with regards to a ceiling ratio that reflects the decision maker's maximum willingness to pay (WTP) for a health gain. The decision rule for an economic evaluation can therefore be expressed as:

$$\frac{\Delta C}{\Delta E} < \lambda$$

where λ equals WTP, and means that if the ICER of an intervention is below the ceiling ratio, introducing the intervention represents good value for money.

Economic evaluations are often based on decision models (such as decision trees, Markov models etc) that calculate results based on various input parameters. There are always uncertainties related to the values of these parameters, making sensitivity analyses an important feature of any economic evaluation. In short, sensitivity

analysis illustrates how much the results vary when model parameters are being changed.

An important kind of sensitivity analysis is referred to as probabilistic sensitivity analysis (PSA), where uncertainty in many model-parameters are taken into account simultaneously. The basic approach in PSA is to assign appropriate probability distributions to the model-parameters, which makes it possible to recalculate the model a certain number of times by values generated by random draws from the distributions. Doing this repeatedly, with a definite number of iterations, makes it possible to estimate probabilities of alternatives being cost-effective subject to different ceiling values of WTP. PSA is often presented as scatterplots, which show point estimates of the ICER for all iterations in the cost-effectiveness plane. Another useful graph, is the cost-effectiveness acceptability frontier (CEAF) that shows, for varying values of WTP, which is the cost-effective option, and the probability of this.

PSA may also be used to produce expected value of perfect information (EVPI). This provides information about the societal value of having more accurate information about the input parameters, which subsequently may be used to inform which parameters on which it would be most useful to get new and improved data. The ranking of EVPI for different parameters (called EVPPI) is dependent on the threshold willingness to pay. If EVPI is to be compared between different patient groups, the ranking is also dependent on the number of patients in each group.

In short, making a model probabilistic, means that it is possible to estimate the uncertainty in decisions of implementing alternative interventions, and also provides a possibility of estimating the value of collecting additional information from new research.

PRIORITY SETTING CRITERIA

According to Norwegian policy documents (4;5), a treatment should be prioritised if the following criteria are met:

1. *The disease is severe;* A disease is considered severe to the degree that it causes pain and discomfort, loss of physical, psychological and social function and if it limits the individual in his or her daily activities. Severity is also evaluated according to the risk increase the disease entails in terms of death, disability and discomfort, if treatment is postponed.

2. *The treatment is effective;* the patient should be expected to benefit from treatment in terms of longevity or improved quality of life of certain duration. The treatment effectiveness should also be well documented.

3. *The treatment is cost-effective;* the added costs of the treatment should be reasonable compared to the added benefits.

The policy documents mentioned above give no guidance as to what constitutes a ”reasonable” relationship between costs and effectiveness. The Directorate of Health however, has recently (in 2007) recommended a preliminary estimate of NOK 500 000 per statistical life year in full health (6), with a probable range between 350 000 and 1 000 000. However, there exists no academic consensus regarding this threshold value, nor has it been subject to a political process, and it can therefore be regarded only as a tentative suggestion.

Clinical efficacy

METHODS

Literature search

We performed a systematic search in OVID-Medline (1950-present) and OVID-Embase (1980-present) on 08.02.2010 and rerun on 15.03.2011. The search was built around the pharmaceutical drugs to be compared; prasugrel and clopidogrel. We limited the search to randomised controlled trials.

Search strategy in Embase (number of hits in parentheses):
1 prasugrel.mp. or exp prasugrel/ (674)
2 efient.mp. (12)
3 1 or 2 (675)
4 limit 3 to "treatment (2 or more terms high specificity)" (198)

Search strategy in Medline (number of hits in parentheses):
1 prasugrel.mp. (270)
2 efient.mp. (2)
3 1 or 2 (270)
4 limit 3 to "therapy (optimized)" (90)

Inclusion criteria

We included clinical trials which were published in full-text and fulfilled the following criteria:

Population:	Patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI)
Intervention:	Prasugrel
Comparator:	Clopidogrel
Outcome:	Death, urgent target vessel revascularization (UTVR), acute myocardial infarction (AMI) and bleeding events
Study design:	Randomised controlled trials

Languages: There were no linguistic limitations during the search, but we only included articles in English or Scandinavian languages and articles with English abstract.

Selection of articles

Two persons (TR and TW) independently reviewed all citations generated by the search to identify potentially relevant articles based on title and/or abstract. Full text versions were obtained for articles appearing to meet the inclusion criteria or in cases where sufficient information was not available to make a decision about inclusion. Two persons independently assessed whether the article was relevant or not according to inclusion criteria. Disagreements were resolved by discussion or by consulting a third reviewer.

Articles meeting the predefined inclusion criteria were assessed for risk of bias for randomised controlled trials (7). All assessments were performed and agreed upon by two persons (TW and TR). Final assessments are available in appendix 1.

Data extraction and data synthesis

The data extraction was performed by two reviewers independently and then compared. We extracted data on the outcomes death (cardiovascular), AMI, UTVR and bleeding events from the included articles.

When possible, we performed meta-analysis using a random effects model. As far as possible our analyses of efficacy and safety are performed according to the principle of "intention-to-treat". Meta-analyses, presented as forest plots, are available in appendix 2.

Grading the evidence

Two reviewers assessed overall confidence in the results for each outcome by using GRADE (Grading of Recommendations, Assessment, Development and Evaluation, www.gradeworkinggroup.org). The method is based on the study design used and involves an evaluation of eight criteria for each outcome. Limitations in any of five criteria may lower the quality: study quality/risk of bias, consistency between trials, directness (in how similar the population, intervention, and outcomes are between the trials and the stated objectives of this report), precision of the estimates and publication bias (likelihood of studies with negative results not published). However, there are also three criteria to evaluate an increase in quality: large effect, plausible confounding would change (lower) the effect and presence of a dose-response gradient. Finally, the overall quality of the evidence for each outcome was categorized as high, moderate, low or very low (see Table 1).

Table 1 GRADE gives the following definition of the different classes of evidence

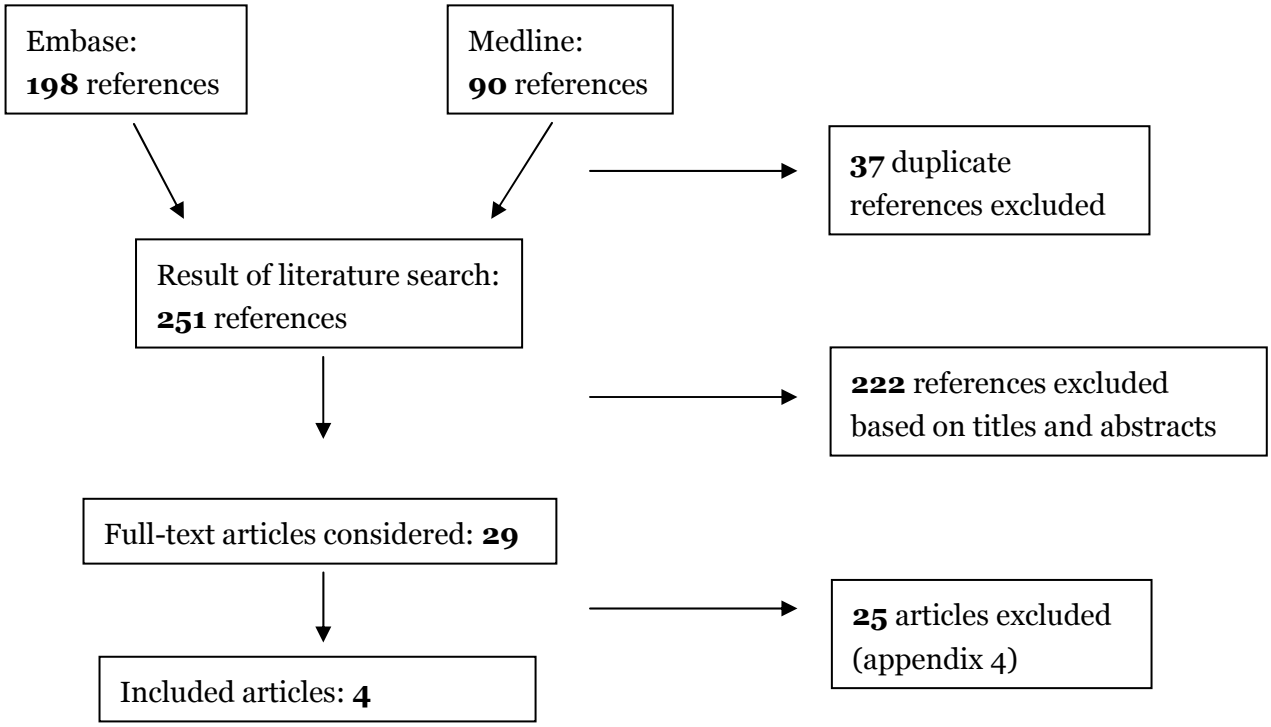
Grade	Definition
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

RESULTS

Result of literature search

We found 251 references in Medline and Embase in the search in February 2010. Of these, only 4 were included. The search was rerun in March 2011 and identified 149 additional references. However, only two systematic reviews met our inclusion criteria (8;9) and neither presented data beyond what we already had included.

Figure 1 Flowchart of identification of documentation



Description of included studies

We included four publications denoting three different studies. The studies are known as JUMBO (10), PRINCIPLE (11) and TRITON (2;12). The studies included

patients who were candidates for planned or urgent PCI. In JUMBO, three different dose regimens of prasugrel (40mg+7.5mg, 60mg+10mg and 60mg+15mg) were compared to clopidogrel (300mg+75mg) for 30 days. In PRINCIPLE, prasugrel (60mg+10mg) was compared to high dose clopidogrel (600mg+150mg) in a cross-over trial, where we use data from the first 15 days before cross-over. Finally, in TRITON, prasugrel (60mg+10mg) was compared to clopidogrel (300mg+75mg) in long-term use for up to 15 months. In all trials both study drugs were given as a higher loading dose followed by a maintenance dose given once daily.

The application for reimbursement to NoMA was based on the TRITON trial, which was also clearly the biggest trial (see table 2).

A full description of the included studies, regarding population, intervention, comparison and outcomes addressed is given in appendix 1. Similarly the evaluation of risk of bias is added for each study in the same appendix.

Table 2 *Overview of included studies*

Study	Number of patients	Treatment time (= follow-up period)	Comparison (loading dose/maintenance dose)
JUMBO (10)	904	30 days	Prasugrel (40 mg / 7.5 mg) Prasugrel dose (60 mg / 10 mg) Prasugrel (60 mg / 15 mg) Clopidogrel (300 mg / 75 mg)
PRINCIPLE (11)	201 (112 with PCI)	30 days (15 days cross-over)	Prasugrel (60 mg / 10 mg) Clopidogrel (600 mg / 150 mg)
TRITON (2;12)	13 608	30 days / 15 months	Prasugrel (60 mg / 10 mg) Clopidogrel (300 mg / 75 mg)

As can be seen from table 2, three different dosing regimens of prasugrel has been studied. Because the only available doses in Norway are 5 mg and 10 mg, we focused the grading of evidence only on data comparing prasugrel 60/10 with clopidogrel 300/75. Meta-analyses were however performed on all data (with each dose separately).

Results of efficacy and safety – short term (30 days)

We extracted data from the included studies and performed meta-analysis where possible. Data are presented by the different prasugrel doses and as a combined estimate for all doses used. See appendix 2 for details. In this report short term is defined as a treatment time or follow-up for up to 30 days.

From the PRINCIPLE study (11) we were only able to use data on mortality. For other outcomes it was not specified whether the patient had undergone PCI or not.

Based on evaluation of risk of bias for each individual study, results from the meta-analysis and using the computer programme GRADEpro, we assessed the overall quality of the evidence for each outcome. A full evidence profile of the results and evaluations is available in appendix 3.

The overall efficacy and safety results and grading of quality of evidence for prasugrel (60mg/10mg) compared to clopidogrel for up to 30 days are presented in Table 3. Results show that prasugrel is significantly more effective in reducing myocardial infarction and rates of UTVR compared to clopidogrel. The quality of the evidence for these two outcomes are high and low, respectively. Hence, we have more confidence in the result for myocardial infarction than the result for UTVR. The use of prasugrel did however also result in a significant increase in bleedings, which was graded as a result with moderate quality of the evidence.

Table 3 *Results of prasugrel compared to clopidogrel, short-term (0-30 days)*

Outcome	Studies	Events / patients		RR (95 % CI)	Quality
		Prasugrel	Clopidogrel		
Death – cardiovascular	3	62/7068	78/7106	0,79 (0,57-1,10)	Low
Myocardial infarction	2	337/7013	432/7049	0,75 (0,65 – 0,86)	High
UTVR	1	58/6813	109/6795	0,53 (0,39 – 0,73)	Low
TIMI* major or minor bleeding	2	179/7013	145/7049	1,24 (1,00 – 1,54)	High

*TIMI (Thrombolysis in Myocardial Infarction) is a group who has classified bleeding. [1]

Results of efficacy and safety – long-term (until 15 months)

For long term treatment with prasugrel *versus* clopidogrel, all data are extracted from only one study, TRITON (2). In this study, follow-up was up to 15 months. With only one study, we could not combine studies in a meta-analysis. However, the data was processed in the same software (Review Manager) as short term data to get a uniform display of results, see appendix 2 for details.

Based on evaluation of risk of bias, results from the study and using the computer programme GRADE, we assessed the overall quality of the evidence for each outcome. A full overview of the results and evaluations done is available in appendix 3.

[1] TIMI major bleeding involves a hemoglobin drop >5 g/dL (with or without an identified site) or intracranial hemorrhage or cardiac tamponade. TIMI minor bleeding involves a hemoglobin drop >3 g/dL but ≤5 g/dL, with bleeding from a known site or spontaneous gross hematuria, hemoptysis, or hematemesis.

The overall efficacy results and grading of the overall quality of evidence for prasugrel (60mg/10mg) compared to clopidogrel for the period between PCI and up to 15 months after PCI are presented in Table 4.

Table 4 *Results of prasugrel compared to clopidogrel, long-term (0 - 15 months)*

Outcome	Studies	Events / patients		RR (95 % CI)	Quality
		Prasugrel	Clopidogrel		
Death – cardiovascular	1	133/6813	150/6795	0,88 (0,70 – 1,11)	Moderate
Myocardial infarction	1	475/6813	620/6795	0,76 (0,68 - 0,86)	Moderate
UTVR	1	156/6813	233/6795	0,67 (0,55 – 0,82)	Moderate
TIMI major or minor bleeding	1	303/6741	231/6716	1,31 (1,10 – 1,55)	Low

In addition to performing meta-analyses of what happens to patients in the 15 month follow-up period after PCI (between 0 months and 15 months), we have performed separate analyses with data for the period between 1 month and 15 months. In these analyses short term TRITON data were subtracted from long term data to give the efficacy and safety results given in table 5. Results based on this analysis were assumed to have one level lower in GRADE, due to loss of directness.

Table 5 *Results of prasugrel compared to clopidogrel (1-15 months)*

Outcome	Studies	Events / patients		RR (95 % CI)	Quality
		Prasugrel	Clopidogrel		
Death – cardiovascular	1	71/6813	72/6795	0,98 (0,71 – 1,36)	Low
Myocardial infarction	1	151/6813	188/6795	0,80 (0,65 - 0,99)	Low
UTVR	1	98/6813	124/6795	0,79 (0,61 – 1,03)	Low
TIMI major or minor bleeding	1	128/6741	89/6716	1,43 (1,10 – 1,87)	Very low

Efficacy of prasugrel (60mg/10mg) compared to clopidogrel in a long term perspective is statistically significant for both myocardial infarction (RR=0,76, CI=0,68-0,86) and UTVR (RR=0,67, CI=0,55-0,82), both at moderate quality of the evidence. When excluding data from the first month after PCI, prasugrel was still significant for preventing myocardial infarctions (RR=0,80, CI=0,65-0,99). However, the effect of prasugrel on reducing UTVRs was only significant the first month.

Safety of clopidogrel was significantly better than that of prasugrel when considering bleeding, regardless of whether the analysis was performed on the period 0-1 month

(RR=1,24, CI=1,0-1,54), 0-15 months (RR=1,31, CI= 1,10-1,55) or 1-15 months (RR=1,43, CI=1,10-1,87) after PCI (high, low and very low quality of the evidence, respectively).

Economic evaluation

METHODS

Model of cost-effectiveness of coronary artery disease (MOCCA)

We used the MOCCA model to calculate the cost-effectiveness of prasugrel compared to clopidogrel for patients with ACS undergoing PCI. This model is originally constructed to analyse the use of drug eluting stents (DES) versus bare metal stents (BMS) for myocardial infarction and angina. MOCCA is partly based on a report published by Norwegian Knowledge Centre for the Health Services in 2004 (13). In addition, the model was updated and redeveloped for a scientific article regarding the discussion of cost-effectiveness of DES versus BMS (1).

MOCCA is a Markov model which follows patients in the period from PCI's are conducted until all are either dead or 100 years old. Patients were assumed to use prasugrel or clopidogrel in combination with acetylsalicylic acid (ASA) in the period after a PCI and for the following 12 months. The model calculates life years gained and costs related to coronary artery disease with the different strategies.

We do not have published Norwegian registries reporting events after PCI. Data on probability of events were based on registry data from the registries SCAAR (Swedish Coronary Angiography and Angioplasty Registry) (14-16) and WDHR (Western Denmark Heart Registry) (17).

The cycle length in MOCCA is half a year throughout the model, based on the fact that the risks of subsequent events are severely increased in the first half year after a PCI, as compared to the subsequent periods. Events in the first half year include either acute myocardial infarction (AMI), UTVR or death (figure 2). Death is in the model divided into cardiovascular and other deaths.

In addition, each intervention (PCI and coronary artery bypass graft (CABG)) is subject to a small probability of procedure related death (0.002 for PCI and 0.018 for CABG) (18). More details on the model can be found in (1).

MOCCA is presented in figure 2. Here, boxes with dotted lines are events, and the others are health states. Each event is denoted with an arrow. The only addition to this model compared to the previous (1) is the addition of bleeding (see next chapter).

Figure 2 Outline of the model structure

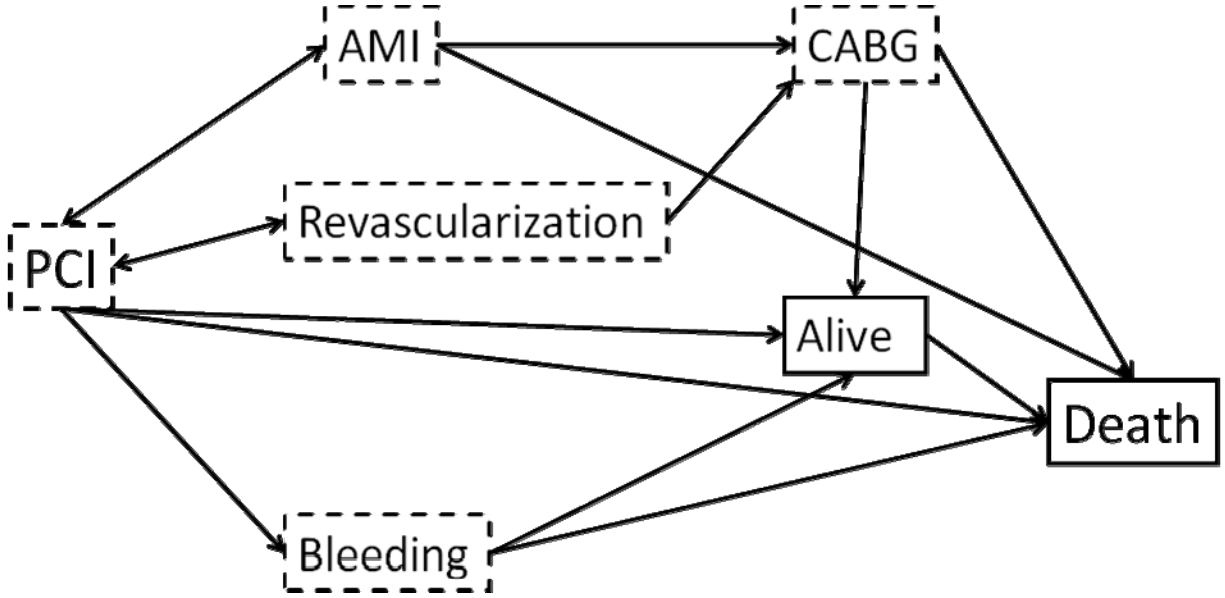


Table 6 Original probabilities of events in MOCCA (taken from article (1))

Probability	Value	Confidence interval	Data source
AMI the first 6 months	0.0639	(0.6-0.68)	SCAAR-data (16)
AMI after 6 months*	0.0161	(0.0147-0.0175)	Based on 6-30 months SCAAR data (16)
CABG when having later AMI	0.2195	(0.213-0.226)	Numbers taken from NTKF register, NCS and NPR (presentation)
Dying during CABG	0.008	(0.005-0.011)	Data from Feiring Heart Clinic (19)
Probability that a UTVR is CABG	0.2195	(0.213-0.226)	Numbers taken from NTKF register, NCS and NPR (presentation by Øystein Vengen)
Dying first 6 months after AMI*	0.0316	(0.029-0.035)	SCAAR data (16)
Dying per 6 month period after the first 6 months*	0.0103	(0.0093-0.0113)	Based on 6-30 months SCAAR data (16)
Dying during PCI-procedure	0.005	(0.003-0.007)	Data from Feiring Heart Clinic (19)
UTVR first 6 months	0.0198	(0.158-0.171)	WDHR data (17)

*6-month probability

Changes and additions to the model

The MOCCA model was originally constructed for analysing all patients undergoing PCI, both ACS patients, and stable coronary artery disease (CAD) patients. Because the scope of this report is to analyse ACS patients only, probabilities of events has to be somewhat adjusted to fit this cohort. Data from the SCAAR registry indicate a somewhat higher mortality after PCI for ACS patients compared to stable CAD patients (20). Based on data from this SCAAR article, we calculated relative risks of death within one and four years for patients with ACS compared to patients with either ACS or stable CAD (1-year; 1.17, 4-year; 1.10). These relative risks were assumed to apply to the risks of death, myocardial infarction and revascularisation.

We added the probability of bleeding into the model as an event after PCI. The event has a 27 month probability of 0.307 % (21), which translates into a 0.068 % half-year probability of bleeding assuming that the risk is constant throughout the 27 month period. Bleeding was again associated with a 0.2% yearly additional risk of dying.

The efficacy and safety of prasugrel (60mg/10mg) compared to clopidogrel is based on our systematic review of the literature. We chose to base our analysis on efficacy of prasugrel 60/10 because the other doses analysed in our clinical evaluation are not available in Norway. Efficacy and grading are based on tables 3, 4 and 5 and ln(RR) and ln(SE) is calculated for use in log-normal distributions in MOCCA (tables 7 and 8). Confidence intervals are used to estimate ln(SE) for all efficacy parameters. The common method for this estimation is based on how these confidence intervals are constructed: $\ln(SE)=(\ln(UL)-\ln(LL))/2Z$, where UL is the upper limit of the confidence interval, LL is the lower limit, and Z is 1,96. Because the confidence intervals are two-sided 95% confidence intervals, 1,96 is used.

For outcomes where quality of the evidence is graded to be “high”, we have used exactly the approach described in the previous paragraph to estimate ln(SE). To incorporate our trust in the evidence into the model, the approach is somewhat modified for outcomes with lower quality of the evidence. If Z in the approach is decreased, then ln(SE) will be bigger. Hence, we have used smaller Z values in this formula because there is uncertainty about how precise the efficacy estimates are. For moderate and low quality, we have used Z values of 1,64 and 1,28 which reflects that we have less trust in the evidence. These values correspond to 90% and 80% confidence intervals.

Table 7 Efficacy of prasugrel compared to clopidogrel, short term (0-30 days)

Outcome	RR (95 % CI)	LN(RR)	LN(SE)*	Quality
Death – cardiovascular	0,79 (0,57 – 1,10)	-0,49	0,39	Low
Myocardial infarction	0,75 (0,65 – 0,86)	-0,36	0,14	High
UTVR	0,53 (0,39 – 0,73)	-0,42	0,24	Low
TIMI major or minor bleeding	1,24 (1,0 – 1,54)	-0,09	0,19	High

*LN(SE), which is the natural logarithm of the standard error, is calculated from the confidence interval and adjusted based on quality of the outcome

Table 8 Efficacy and safety of prasugrel compared to clopidogrel, long term (1-15 months)

Outcome	RR (95 % CI)	LN(RR)	LN(SE)*	Quality
Death – cardiovascular	0,98 (0,71 – 1,36)	-0,02	0,25	Low
Myocardial infarction	0,80 (0,65 - 0,99)	-0,22	0,16	Low
UTVR	0,79 (0,61 – 1,03)	-0,24	0,20	Low
TIMI major or minor bleeding	1,43 (1,10 – 1,87)	0,36	0,26	Very low

*LN(SE) is calculated from the confidence interval and adjusted based on quality of the outcome

None of the studies reported efficacy or safety after more than 15 months. Because our model was designed to model half-year periods, we used the short term relative risks as efficacy data for the first period, the long term data for the second half year period, and half of the long term efficacy for the third time period (from 13 to 18 months). After that, we assumed no effect of prasugrel compared to clopidogrel.

Efficacy estimates on all outcomes from tables 7 and 8 were included into the model. These efficacy estimates were then attached to the probabilities of events for the periods specified in the previous paragraph. Based on this, life year projections and lifetime costs were estimated.

All costs were measured in Norwegian Kroner (NOK, 2008) and presented in table 9. All future costs and effects were discounted at a rate of 4% per year according to Norwegian guidelines (22). Costs of prasugrel and clopidogrel are only added the first year.

Table 9 Costs (NOK) related to events and health states

Description	Time	Value (NOK)
AMI treatment costs including PCI	Per procedure	104 667
Cost of having asymptomatic CVD	Per year	4 731
Costs related to having CABG	Per procedure	186 524
Costs related to bleeding	Per event	34 221
Costs of clopidogrel 75 mg	Per year	4 963
Costs of prasugrel 10 mg	Per year	6 805
Costs of PCI	Per procedure	38 228

Probabilistic model and analyses

The model (MOCCA) was created as a probabilistic model. This means that all uncertain parameters (efficacy, costs, epidemiological data etc.) were modelled as probability distributions rather than point estimates. We then drew 1 000 values from each of these distributions (Monte Carlo simulation) and calculated the remaining life expectancy and lifetime costs 1 000 times.

In the results we first present the mean of these simulations as a "base case". Then we plot the incremental costs and effects in a "cost-effectiveness plane" to show the variations regarding the decision. Third, we present results as cost-effectiveness acceptability frontier, that express which alternative that is more cost-effective for a range of willingness to pay for health thresholds, and the corresponding probability of this based on simulations. Finally, we performed value of information analysis for the parameters. In this analysis, we explore the uncertainty surrounding specific groups of parameters; costs, efficacy (and safety) and probabilities (mainly epidemiological data). The expected value of perfect information for parameters (EVPPI) gives the expected costs of totally eradicating the uncertainty surrounding each group of parameters, based on given thresholds for cost-effectiveness. We did not perform one-way sensitivity analyses on parameters with uncertainty, because this method has some problems. These problems are specifically given in an article by Karl Claxton (23).

RESULTS

In the base-case, prasugrel resulted in 0,21 more life years and increased lifetime cost with NOK 8 100 (discounted) compared to clopidogrel, which gives an incremental cost-effectiveness ratio (ICER) of NOK 37 600 per life year (table 10).

Table 10

Duration of efficacy	Incremental costs	Incremental effectiveness	ICER
15 months	8 100	0,21	37 600

Monte Carlo simulations show that prasugrel is the more cost-effective strategy in 88% of 1 000 simulations (see table 12 and figure 3). In the figure, the dotted line represents one possible threshold for cost-effectiveness (willingness-to-pay (WTP)), here set at NOK 500 000 per life year gained. In table 12, we have listed how many of the simulations that are in each quadrant of the plot, and for the upper right (I) and lower left (III) quadrants, we have also listed the proportion of simulations below and above the WTP-line (components C2 and C3 below).

Figure 3 Scatter plot of simulations of prasugrel compared to clopidogrel

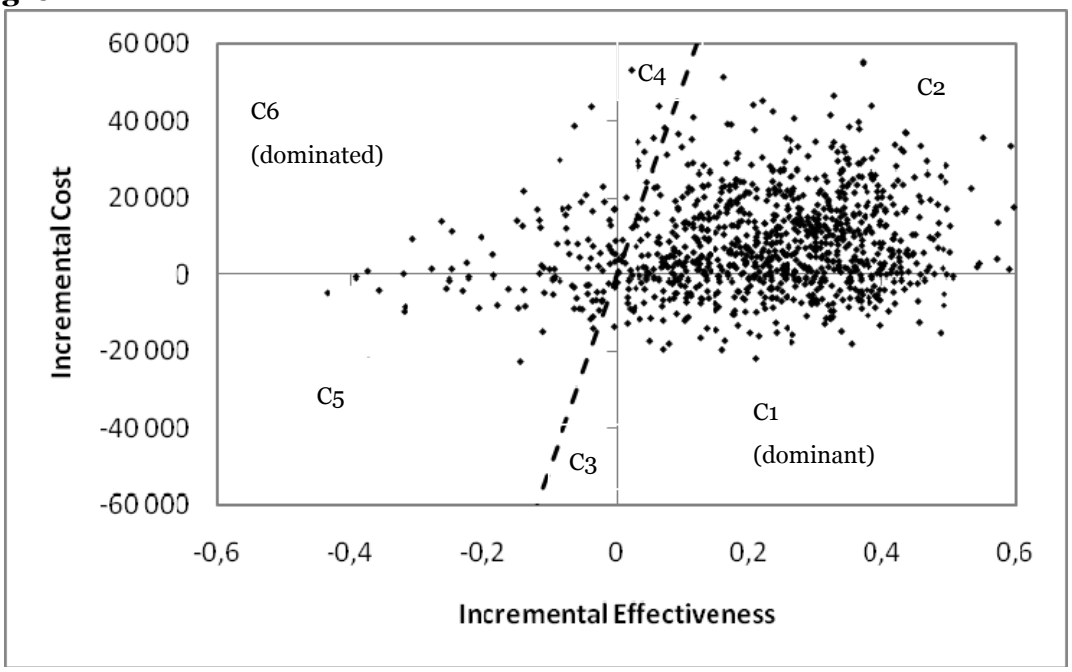


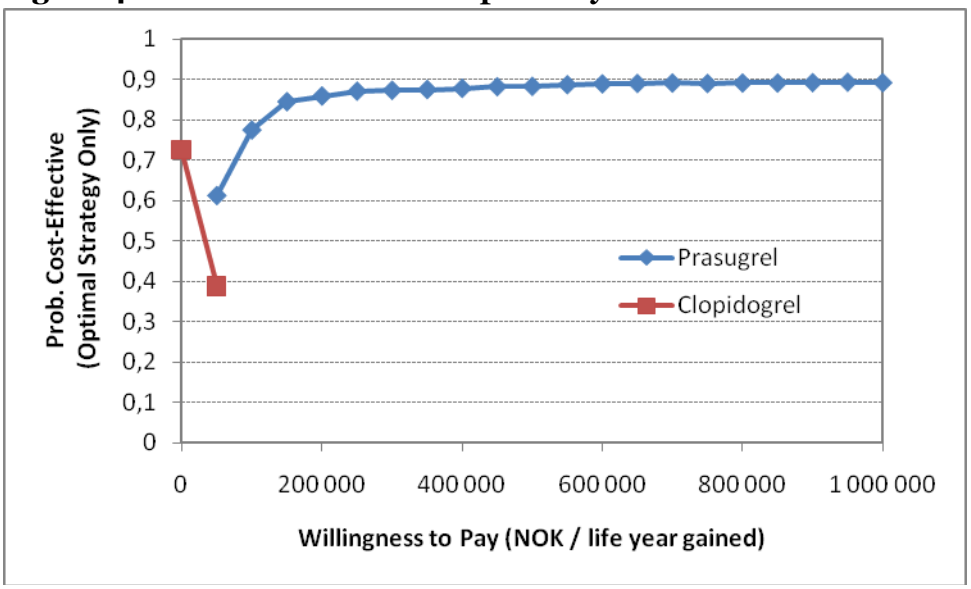
Table 11 Percentages in each quadrant of figure 2

Component	Quadrant	Incr. Eff.	Incr. Cost	ICER	Percent
C1	IV	IE > 0	IC < 0	Superior	22,7%
C2	I	IE > 0	IC > 0	< 500 000	65,3%
C3	III	IE < 0	IC < 0	> 500 000	0,3%
C4	I	IE > 0	IC > 0	> 500 000	1,6%
C5	III	IE < 0	IC < 0	< 500 000	4,4%
C6	II	IE < 0	IC > 0	Inferior	5,7%

The WTP-line in figure 3 is not defined in Norway. Hence, we have plotted a cost-effectiveness acceptability frontier (based on the simulations from figure 3), which gives the probability of cost-effectiveness for the more cost-effective strategy for varying WTP's (figure 4). From this figure, one can see that the cheapest drug

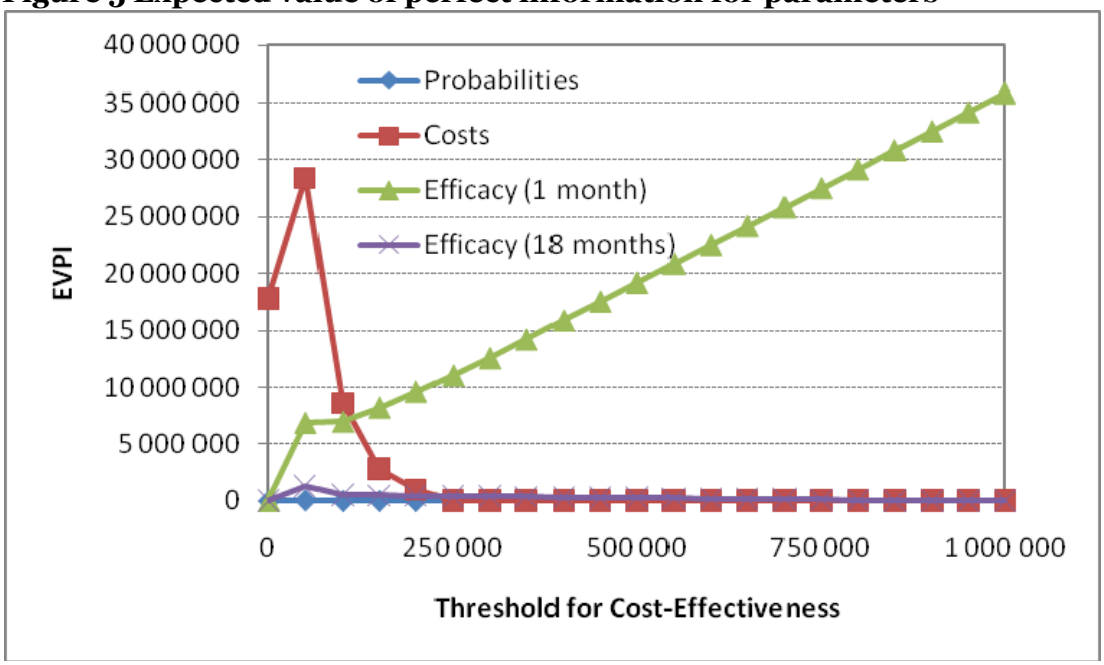
(clopidogrel) is likely to be cost-effective when WTP is low, while prasugrel is likely to be cost-effective for WTP above approximately NOK 50 000 per life year gained.

Figure 4 Cost-effectiveness acceptability frontier



We also performed value of information analyses to detect which type of parameters that had the biggest impact on decision uncertainty (figure 5). These analyses suggested that for WTP in ranges suggested for Norway (NOK 350 000 – NOK 1 000 000), short term efficacy and safety parameters influence the uncertainty the most. Specifically, the EVPI for short term efficacy and safety parameters was NOK 19 million for a willingness to pay of NOK 500 000 and given a patient population of 8 500.

Figure 5 Expected value of perfect information for parameters



Scenario analyses

We also performed scenario analyses to test the assumption of duration of efficacy in our model. Long term efficacy and safety documented in the TRITON trial (2) was reported after 15 months. So instead of ending the effect at 15 months, we extended the effect to last for the remainder of the lifetime. If the efficacy from prasugrel lasts for the remaining of a person's lifetime, the increased effectiveness will be 0,31 life years and lifetime costs will be 12 000 lower with prasugrel (Table 12), which is usually called a dominant result (increase effectiveness and reduce costs). We also tried to analyse the model only looking at effect during the 12 months in which the patients were treated. This analysis resulted in 0,22 life years gained and an increase in lifetime costs of NOK 8 300, which gives a cost-effectiveness ratio of NOK 37 900 per life year gained, which also is below the suggested willingness to pay of NOK 500 000 per life year gained.

Table 12 Prasugrel compared to clopidogrel for different durations of therapy

Duration of efficacy	Incremental costs	Incremental effectiveness	ICER
12 months	8 300	0,22	37 900
15 months	8 100	0,21	37 600
Remaining lifetime	-12 200	0,31	dominant

Discussion

In this health technology assessment, we have summarised efficacy and safety for the comparison between prasugrel and clopidogrel for patients with ACS undergoing PCI. In addition, we have performed an economic evaluation concerning the cost-effectiveness between the two medications.

In the systematic review of efficacy, we found that prasugrel significantly decreased rates of UTVR and myocardial infarction compared to clopidogrel both in short term and long term (high, moderate and low quality of evidence). Relating to safety, prasugrel increases bleeding in both short and long term compared to clopidogrel (high and low quality of the evidence). The studies revealed no significant difference in mortality (low and moderate quality of the evidence).

The threshold for willingness to pay in Norway is not defined, but one suggestion is that it may be in the range between 350 000 and 1 000 000 (6). At an incremental cost-effectiveness ratio of NOK 37 600 per life year gained, prasugrel is clearly cost-effective compared to clopidogrel for ACS patients undergoing PCI. There is however some uncertainty around this estimate; prasugrel is cost-effective only in 88% of the simulations at a willingness to pay of NOK 500 000. Hence, parameter uncertainty is considerable. This parameter uncertainty related to clinical trial data seems to have the biggest impact, mainly due to lack of long term clinical trials.

There are substantial possibilities of overestimating effectiveness of interventions if efficacy data are applied for the whole life span. Hence, we have only included efficacy data for the first 15 months in our base case analyses. If efficacy/safety is assumed to be life-long, prasugrel would be dominant compared to clopidogrel (save cost and increase life-expectancy). These analyses confirmed that there are substantial differences in cost-effectiveness if effectiveness is assumed to be life-long.

In long term meta-analyses, 283 cardiovascular deaths were observed in a population of 13608 patients, but this was insufficient to show any statistical difference in mortality between prasugrel and clopidogrel. In our value of information analysis, we found that data on short term efficacy is the type of data where it is most useful to conduct further research at an expected value of perfect information of NOK 19 million.

In our report we have only investigated whether the health effects related to prasugrel treatment is worth the cost compared to clopidogrel. Yearly, there are approximately 8 500 patients who are eligible for prasugrel treatment. Hence, the one year medication cost of changing from clopidogrel (NOK 4 963 p.a.) to prasugrel (NOK 6 805 p.a.) would be NOK 15,7 million.

Other economic evaluations

We found only one other economic evaluation of prasugrel versus clopidogrel, performed by Mahoney and co-workers (24). Their results showed a somewhat lower increase in life-expectancy (0,102) and a reduction in lifetime costs (-$221) with prasugrel compared with clopidogrel in a US setting. Hence, this analysis resulted in prasugrel being a dominant strategy (less costly and more effective). It seems as they adopted a similar duration of the effectiveness of prasugrel as in our analysis, which led to a similar increase in life expectancy (0.10 compared to 0.21). The differences are probably due to the fact that the US model was based on patient level data and life expectancy was hence modeled somewhat different from our model.

Limitations in our analysis

We included UTVRs, AMI, bleeding and death as events in the model while restenosis and major adverse cardiac event (MACE) were excluded. Stent thrombosis was not included because most patients with stent thrombosis will also have an AMI and/or a UTVR. MACE is a composite endpoint of mainly the included events, and was not included because it is not specific enough to be used in a health economic model.

In our MOCCA model, only the probability of death is age dependent. Other transition probabilities may as well be age dependent, but lack of data did not allow us to model such age dependency which may be a limitation of this work.

Amounts of health services used in different health states in the model are based on expert judgements (personal communication: Ivar Sønbø Kristiansen). This may not correctly represent the average cost of being in each health state. The uncertainty around these parameters has however been incorporated into the sensitivity analysis and further explored in analysis of expected value of perfect information of parameters (EVPPI). These analyses indicate that it is not worthwhile to use more effort to increase the precision around these cost estimates.

The clinical trials included in the meta-analyses were performed in 2, 4 and 30 different countries, not including Norway. Whether these were comparable to Norway has not been assessed. It is unlikely that the patient populations in this trial completely reflect the Norwegian population which is eligible for treatment with prasugrel. It is unclear to what extent this influences our results. Usually, however, rela-

tive effects are comparable across countries, and then this concern would not be an issue.

Our meta-analyses give somewhat conflicting results for different doses of prasugrel. Whether cost-effectiveness analyses with other doses would give other results is hard to tell. We did however base our analysis on the doses that are reimbursed in Norway (10 mg prasugrel and 75 mg clopidogrel).

Our model analyses are based on a health care sector perspective. If a societal perspective was chosen, it is reasonable to assume that prasugrel would be more cost-effective due to avoidance of indirect cost implications. Hence, that would not alter the conclusions from these analyses.

Health related quality of life was not included in the model. The model has only one alive health state, so the only relevant health related quality of life decrement would be related to that health state relative to a normal population or to the events. The events are usually treated quickly, and hence they will not have any great impact on lifetime cost-effectiveness. If quality of life is included for only one health state, that would decrease the values of the benefits from our analysis, but only by a small amount (25).

Because some sub-groups of ACS patients have higher risk of clinical events after PCI (e.g. STEMI patients and patients with diabetes), it might be an idea to conduct separate analyses on these groups. Studies have however shown that these groups may have greater efficacy than the whole group of ACS patients (26;27), hence these analyses would most likely result in prasugrel being even more cost-effective, which will not change our conclusions.

Conclusions

Prasugrel (60mg/10mg) significantly lowers rates of AMI and UTVRs after PCI in ACS patients, but fails to show significant reduction in mortality rates compared to clopidogrel. However, prasugrel shows significant increase in rates of bleeding compared to clopidogrel. Quality of the evidence for these outcomes ranged between low and high.

Prasugrel is likely to be cost-effective compared to clopidogrel for ACS patients undergoing PCI, but the simulations show that this result is uncertain irrespective of level of willingness to pay for health.

NEED FOR FURTHER RESEARCH

The need for further research is explored through value of information analysis. This analysis indicates that to conduct further research on efficacy data, would have the biggest impact on decreasing decision uncertainty. There is especially a need for further clinical trials exploring mortality with prasugrel compared to clopidogrel in the short term.

IMPLICATIONS FOR PRACTICE

Our analysis has incorporated both positive and negative clinical effects of prasugrel compared to clopidogrel. When taking into account both health effects and costs related to these events, our analysis indicates that it is worth the cost to the health care sector to give reimbursement to prasugrel in the Norwegian setting.

References

Reference List

1. Wisløff T, Atar D, Kristiansen IS. Cost-effectiveness of drug eluting stents as compared to bare metal stents in patients with coronary artery disease. 2010.

2. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357(20):2001-15.

3. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. Methods for the Economic Evaluation of Health Care Programmes. Third. Oxford University Press; 2005.

4. Forskrift om prioritering av helsetjenester, rett til nødvendig helsehjelp fra spesialisthelsetjenesten, rett til behandling i utlandet og om klagenemnd (prioriteringsforskriften). 2004.

5. Lønning II. Prioritering på ny - Gjennomgang av retningslinjer for prioriteringer innen norsk helsetjeneste. NOU 1997: 18.

6. Sælensminde K. Helseeffekter i samfunnsøkonomiske analyser.: Sosial- og helsedirektoratet; 2007 Dec.

7. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions.: The Cochrane Collaboration; 2009. (Version 5.0.2).

8. Bellemain-Appaix A, Brieger D, Beygui F, Silvain J, Pena A, Cayla G, et al. New P2Y12 inhibitors versus clopidogrel in percutaneous coronary intervention: a meta-analysis. J Am Coll Cardiol 2010;56(19):1542-51.

9. Mohammad RA, Goldberg T, Dorsch MP, Cheng JW. Antiplatelet therapy after placement of a drug-eluting stent: a review of efficacy and safety studies. Clin Ther 2010;32(14):2265-81.

10. Wiviott SD, Antman EM, Winters KJ, Weerakkody G, Murphy SA, Behounek BD, et al. Randomized comparison of prasugrel (CS-747, LY640315), a novel thienopyridine P2Y12 antagonist, with clopidogrel in percutaneous coronary intervention: results of the Joint Utilization of Medications to Block Platelets Optimally (JUMBO)-TIMI 26 trial. Circulation 2005;111(25):3366-73.

11. Wiviott SD, Trenk D, Frelinger AL, O'Donoghue M, Neumann FJ, Michelson AD, et al. Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 trial. Circulation 2007;116(25):2923-32.

12. O'Donoghue M, Antman EM, Braunwald E, Murphy SA, Steg PG, Finkelstein A, et al. The efficacy and safety of prasugrel with and without a glycoprotein IIb/IIIa inhibitor in patients with acute coronary syndromes undergoing percutaneous intervention: a TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis In Myocardial Infarction 38) analysis. J Am Coll Cardiol 2009;54(8):678-85.

13. Kløw N-E, Rotevatn S, Steigen T, Vatne K, Kristiansen IS, Wisløff T, et al. [Prevention of restenosis].: Norwegian Health Services Research Centre; 2004. (8).

14. Lagerqvist B, James SK, Stenestrand U, Lindback J, Nilsson T, Wallentin L. Long-term outcomes with drug-eluting stents versus bare-metal stents in Sweden. N Engl J Med 2007;356(10):1009-19.

15. James SK, Stenestrand U, Lindback J, Carlsson J, Schersten F, Nilsson T, et al. Long-term safety and efficacy of drug-eluting versus bare-metal stents in Sweden. N Engl J Med 2009;360(19):1933-45.

16. Long-term outcome of DES vs BMS implanted in Sweden 2003-2004: of the House Comm. on FDA, Lagerqvist B, Wallentin L, Lindbäck J, Nilsson T, James SK, Stenestrand U, (Dec 7, 2006).

17. Kaltoft A, Jensen LO, Maeng M, Tilsted HH, Thayssen P, Bottcher M, et al. 2-year clinical outcomes after implantation of sirolimus-eluting, paclitaxel-eluting, and bare-metal coronary stents: results from the WDHR (Western Denmark Heart Registry). J Am Coll Cardiol 2009;53(8):658-64.

18. Hill R, Bagust A, Bakhai A, Dickson R, Dundar Y, Haycox A, et al. Coronary artery stents: a rapid systematic review and economic evaluation. Health Technol Assess 2004;8(35):1-256.

19. Mølstad P. Survival after percutaneous coronary intervention and coronary artery bypass grafting in a single centre. Scand Cardiovasc J 2007;41(4):214-20.

20. Norhammar A, Lagerqvist B, Saleh N. Long-term mortality after PCI in patients with diabetes mellitus: results from the Swedish Coronary Angiography and Angioplasty Registry. EuroIntervention 2010;5(8):891-7.

21. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324(7329):71-86.

22. Finansdepartementet. Veileder i samfunnsøkonomiske analyser. 2005.

23. Claxton K. Exploring uncertainty in cost-effectiveness analysis. Pharmacoeconomics 2008;26(9):781-98.

24. Mahoney EM, Wang K, Arnold SV, Proskorovsky I, Wiviott S, Antman E, et al. Cost-effectiveness of prasugrel versus clopidogrel in patients with acute coronary syndromes and planned percutaneous coronary intervention: results from the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with Prasugrel-Thrombolysis in Myocardial Infarction TRITON-TIMI 38. Circulation 2010;121(1):71-9.

25. Greenhalgh J, Bagust A, Boland A, Saborido CM, Fleeman N, McLeod C, et al. Prasugrel for the treatment of acute coronary artery syndromes with percutaneous coronary intervention. Health Technol Assess 2010;14 Suppl 1:31-8.

26. Wiviott SD, Braunwald E, Angiolillo DJ, Meisel S, Dalby AJ, Verheugt FW, et al. Greater clinical benefit of more intensive oral antiplatelet therapy with prasugrel in patients with diabetes mellitus in the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-Thrombolysis in Myocardial Infarction 38. Circulation 2008;118(16):1626-36.

27. Montalescot G, Wiviott SD, Braunwald E, Murphy SA, Gibson CM, McCabe CH, et al. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. Lancet 2009;373(9665):723-31.

28. Trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel (TRITON-TIMI 38). ACC Cardiosource Review Journal 2007;16(12):Dec.

29. Prasugrel after angioplasty and stenting: Continue to use aspirin + clopidogrel. Prescrire Int 2009;18(103):2009.

30. Antman EM, Wiviott SD, Murphy SA, Voitk J, Hasin Y, Widimsky P, et al. Early and late benefits of prasugrel in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a TRITON-TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel-Thrombolysis In Myocardial Infarction) analysis. J Am Coll Cardiol 2008;51(21):2028-33.

31. Capranzano P, Ferreiro JL, Angiolillo DJ, Capranzano P, Ferreiro JL, Angiolillo DJ. Prasugrel in acute coronary syndrome patients undergoing percutaneous coronary intervention. [Review] [49 refs]. Expert Rev Cardiovasc Ther 2009;7(4):361-9.

32. Cowley MJK. Developments in antiplatelet therapy for acute coronary syndromes and considerations for long-term management. Current Medical Research and Opinion 2009;25(6):June.

33. Floyd J, Wolfe S, Floyd J, Wolfe S. Prasugrel STEMI subgroup analysis. Lancet 2009;373(9678):1845-6.

34. Khoynezhad AM. Perioperative management of patients on adenosine diphosphate inhibitors in the era of drug-eluting stents: Review of the literature and clinical Implications. Current Medicinal Chemistry 2009;16(5):2009.

35. Mariani M, Mariani G, De Servi S, Mariani M, Mariani G, De Servi S. Efficacy and safety of prasugrel compared with clopidogrel in patients with acute coronary syndromes: results of TRITON-TIMI 38 trials. Expert Rev Cardiovasc Ther 2009;7(1):17-23.

36. Montalescot GS. Prasugrel compared with high-dose clopidogrel in acute coronary syndrome: The randomised, double-blind ACAPULCO* study. Thrombosis and Haemostasis 2010;103(1):January.

37. Morrow DA, Wiviott SD, White HD, Nicolau JC, Bramucci E, Murphy SA, et al. Effect of the novel thienopyridine prasugrel compared with clopidogrel on spontaneous and procedural myocardial infarction in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38: an application of the classification system from the universal definition of myocardial infarction. Circulation 2009;119(21):2758-64.

38. Murphy SA, Antman EM, Wiviott SD, Weerakkody G, Morocutti G, Huber K, et al. Reduction in recurrent cardiovascular events with prasugrel compared with clopidogrel in patients with acute coronary syndromes from the TRITON-TIMI 38 trial. Eur Heart J 2008;29(20):2473-9.

39. O'Donoghue ML, Braunwald E, Antman EM, Murphy SA, Bates ER, Rozenman Y, et al. Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: an analysis of two randomised trials. [Review] [28 refs]. Lancet 2009;374(9694):989-97.

40. Pride YB, Wiviott SD, Buros JL, Zorkun C, Tariq MU, Antman EM, et al. Effect of prasugrel versus clopidogrel on outcomes among patients with acute coronary syndrome undergoing percutaneous coronary intervention without stent implantation: a TRial to assess

Improvement in Therapeutic Outcomes by optimizing platelet inhibitioN with prasugrel (TRITON)-Thrombolysis in Myocardial Infarction (TIMI) 38 substudy. Am Heart J 2009;158(3):e21-e26.

41. Schafer JA, Kjesbo NK, Gleason PP, Schafer JA, Kjesbo NK, Gleason PP. Critical review of prasugrel for formulary decision makers. [Review] [29 refs]. J Manage Care Pharm 2009;15(4):335-43.

42. Serebruany VL, Serebruany VL. Excess rates of nonfatal myocardial infarction in the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel (preventing clinical events or chasing enzymatic ghosts?). Am J Cardiol 2008;101(9):1364-6.

43. Serebruany VL, Serebruany VL. Bleeding risks with prasugrel in the TRITON trial: good news ... bad news. Cardiology 2008;111(4):265-7.

44. Spinler SA, Rees C, Spinler SA, Rees C. Review of prasugrel for the secondary prevention of atherothrombosis. [Review] [71 refs]. J Manage Care Pharm 2009;15(5):383-95.

45. Veverka AH. Prasugrel: A new thienopyridine inhibitor. Journal of Pharmacy Practice 2009;22(2):April.

46. Webster MW, Gladding P, Webster MWI, Gladding P. Prasugrel STEMI subgroup analysis. Lancet 2009;373(9678):1846-8.

47. Wiviott SD, Antman EM, Gibson CM, Montalescot G, Riesmeyer J, Weerakkody G, et al. Evaluation of prasugrel compared with clopidogrel in patients with acute coronary syndromes: design and rationale for the TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet InhibitioN with prasugrel Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38). Am Heart J 2006;152(4):627-35.

48. Wiviott SD, Braunwald E, Murphy SA, Antman EM, TRITON TIMI, Wiviott SD, et al. A perspective on the efficacy and safety of intensive antiplatelet therapy in the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-thrombolysis in myocardial infarction 38. Am J Cardiol 2008;101(9):1367-70.

49. Wiviott SD, Braunwald E, McCabe CH, Horvath I, Keltai M, Herrman JP, et al. Intensive oral antiplatelet therapy for reduction of ischaemic events including stent thrombosis in patients with acute coronary syndromes treated with percutaneous coronary intervention and stenting in the TRITON-TIMI 38 trial: a subanalysis of a randomised trial. Lancet 2008;371(9621):1353-63.

Appendices

APPENDIX 1: CHARACTERISTICS OF INCLUDED STUDIES

PICO for Wiviott et al., 2005 - JUMBO

Wiviott et al., 2005 Randomized Comparison of Prasugrel (CS-747, LY640315), a Novel Thienopyridine P2Y12 Antagonist, With Clopidogrel in Percutaneous Coronary Intervention Results of the Joint Utilization of Medications to Block Platelets Optimally (JUMBO)–TIMI 26 Trial	
Methods	See risk of bias table
Patients	(1) 18 to 75 years of age, (2) be a candidate for elective or urgent PCI with intended coronary stenting, (3) have a native target coronary artery stenosis >60% that was thought by the operator to be amenable to stenting with </=2 approved coronary stents per lesion
Intervention	Prasugrel-low dose (40-mg loading dose followed by 7.5 mg daily), n=199 Prasugrel-intermediate dose (60-mg loading dose followed by 10 mg daily), n=200 Prasugrel-high dose (60-mg loading dose followed by 15 mg daily), n=251 Maintenance therapy was continued for 29 to 34 days. No further follow-up after the 30 day visit (range day 29-35)
Comparisons	Clopidogrel (300-mg loading dose followed by 75 mg daily), n=254
Outcomes measured	*Non–CABG-related "significant hemorrhage" at 30 days, defined as the composite of TIMI major and minor hemorrhage. *Major adverse cardiac event (MACE) components individually and in combination. MACE were defined as any one of the following, occurring through the 30-day visit after PCI: (1) death (all-cause mortality), (2) myocardial infarction (MI), (3) stroke, (4) recurrent myocardial ischemia requiring hospitalization, and (5) clinical target vessel thrombosis (CTVT)
Notes	Conducted between April and December 2003 at 80 sites in the United States and Canada. Concomitant medication: aspirin, unfractionated heparin, GP IIb/IIIa inhibitors at the discretion of the treating physician. Study powered for safety, not efficacy endpoints.

"Risk of Bias" table for Wiviott et al., 2005

Entry	Judgement	Description, Wiviott et al., 2005
Adequate sequence generation?	Unclear	A 4:4:5:5 ratio. Randomisation was stratified on the basis of the investigator's intention to use a glycoprotein (GP)

		IIb/IIIa inhibitor during PCI.
Allocation concealment?	Unclear	Not described,
Blinding? (participants, personell, outcome assessors)	Yes	Double-blind, double dummy Clopidogrel/placebo was over encapsulated. Previous test showed over encapsulated clopidogrel was bioequivalent pharmacokinetically to unencapsulated clopidogrel
Incomplete outcome data adressed?	Yes	All analyses were performed on an intent-to-treat basis of evaluable subjects. An evaluable subject was prespecified as a randomised subject who received at least the loading dose of study drug.
Free of selective reporting?	Unclear	
Free of other bias?	Unclear	Primary analyses were performed by an independent statistician at the contract research organization (Parexel, International) and verified by the sponsor and the TIMI Study Group independently. The TIMI Study Group had possession of and full access to all databases used for the analysis of the trial.
Conclusion	Low risk of bias	

PICO for Wiviott et al., 2007 - PRINCIPLE

Wiviott et al., 2007 Prasugrel Compared With High Loading- and Maintenance-Dose Clopidogrel in Patients With Planned Percutaneous Coronary Intervention The Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation–Thrombolysis in Myocardial Infarction 44 Trial	
Methods	See risk of bias table
Patients	>/= 18 years of age and were scheduled to undergo cardiac catheterization with planned PCI for angina and at least one of the following: coronary angiography within 14 days with at least 1 lesion amenable to PCI, a functional study within 8 weeks with objective findings of ischemia, or prior PCI or coronary artery bypass graft surgery.
Intervention	Prasugrel 60 mg LD before PCI and 10 mg/d MD (until 15 days) after PCI, n=102 (55 with PCI) 15 +/-2 days then crossover without wash-out and another 14+/-2 days No further follow-up after the 29 day visit.
Comparisons	Clopidogrel 600 mg LD before PCI and 150 mg/d MD (until 15 days) after PCI N=99 (57 with PCI)
Outcomes measured	*Pharmacodynamic (several clotting parameters) *Non–coronary artery bypass graft surgery–related TIMI major or minor bleeding until day 15 *Bleeding events reported by investigators *Major adverse cardiac events, including cardiovascular death, myocardial infarction, and stroke occurring during the combined LD and precrossover MD phase.
Notes	Excluded if any thienopyridine within 5 days, glycoprotein(GP) IIb/IIIa inhibitor within 7 days or planned use

	14 investigative sites in 4 countries (France, Germany, Israel and USA)

"Risk of Bias" table for Wiviott et al., 2007

Entry	Judgement	Description, Wiviott et al., 2007
Adequate sequence generation?	Unclear	Not described beyond: Multicenter, randomised, double-blind, double-dummy, active comparator– controlled,
Allocation concealment?	Unclear	Not described,
Blinding? (participants, personell, outcome assessors)	Yes	Description of blinded dosing, blinded lab.personell,
Incomplete outcome data adressed?	No	In every instance, the analyses considered only subjects with evaluable measurements available for a given time point. Generally only 4 of 5 patients were evaluable (see fig 2).
Free of selective reporting?	Unclear	The authors had full access to and take responsibility for the integrity of the data. All authors have read and agree with the manuscript as written.
Free of other bias?	Unclear	
Conclusion	High risk of bias	

PICO for Wiviott et al., 2007 - TRITON

Wiviott et al., 2007 Prasugrel Compared With High Loading- and Maintenance-Dose Clopidogrel in Patients With Planned Percutaneous Coronary Intervention The Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation–Thrombolysis in Myocardial Infarction 44 Trial	
Methods	See risk of bias table
Patients	Patients with acute coronary syndromes with scheduled PCI. Consisted of two strata (1) moderate-to-high-risk unstable angina or non–ST-elevation myocardial infarction; ischemic symptoms lasting 10 minutes or more and occurring within 72 hours before randomisation, a TIMI risk score19 of 3 or more, and either ST-segment deviation of 1 mm or more or elevated levels of a cardiac biomarker of necrosis (2) with ST-elevation myocardial infarction; enrolled within 12 hours after the onset of symptoms if primary PCI was planned or within 14 days after receiving medical treatment
Intervention	Prasugrel LD 60 mg, MD 10 mg daily for up to 15 months (N= 6813, 26%STEMI) No further follow-up specified.
Comparisons	Clopidogrel LD 300 mg, MD 75 mg daily for up to 15 months (N= 6795, 26%STEMI)
Outcomes measured	*Composite of the rate of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. *composite of death from cardiovascular causes, nonfatal myocardial infarction, or urgent target-vessel revascularization. * stent thrombosis *composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or rehospitalisation due to a cardiac ischemic event.

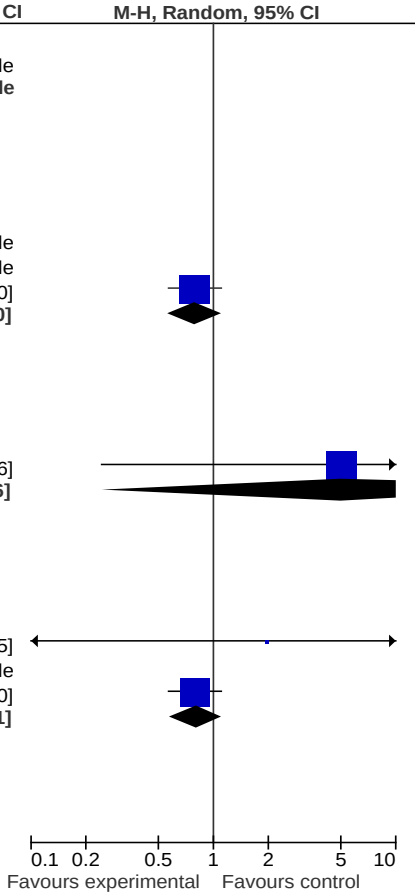
	*TIMI major bleeding not related to coronary-artery bypass grafting (CABG) *non–CABG-related TIMI life-threatening bleeding *TIMI major or minor bleeding
Notes	The choice of vessels treated, devices used, and adjunctive medication administered to support PCI was left to the discretion of the treating physician. Nearly all patients (99%) had PCI at the time of randomisation, 94% received at least one intracoronary stent Aspirin was required, recommended dose 75-162 mg 707 sites, 30 countries (USA, Europe, Canada, South-America, Australia, New Zealand,, South Africa) nov 2004-jan 2007

"Risk of Bias" table for Wiviott et al., 2007

Entry	Judgement	Description, Wiviott et al., 2007
Adequate sequence generation?	Unclear	Not described Quintiles Corporation provided data- and site-management services.
Allocation concealment?	Unclear	Not described
Blinding? (participants, personell, outcome assessors)	Yes	LD was administered, in a double-blind manner, anytime between randomisation and 1 hour after leaving the cardiac catheterization laboratory.
Incomplete outcome data adressed?	Yes	Efficacy comparisons were performed on the basis of the time to the first event, according to the intention-to-treat principle. Safety analyses were carried out on data from patients who received at least one dose of the study drug.
Free of selective reporting?	Unclear	
Free of other bias?	Unclear	The coronary anatomy had to be known to be suitable for PCI before randomisation
Conclusion	High risk of bias	

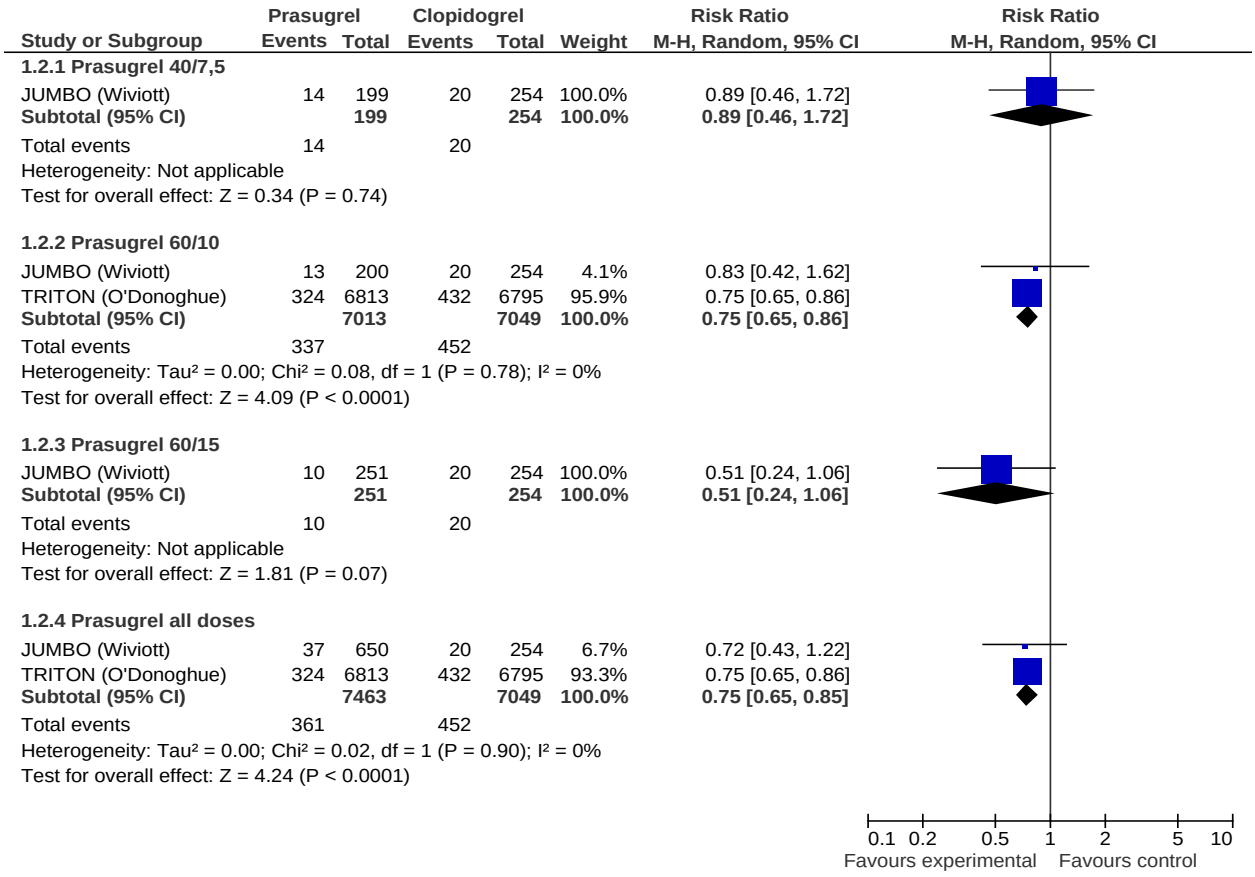
Cardiovascular death short term (14-30 days):

Study or Subgroup	Prasugrel Events	Prasugrel Total	Clopidogrel Events	Clopidogrel Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Prasugrel 40/7,5						
JUMBO (Wiviott)	0	199	0	254		Not estimable
Subtotal (95% CI)		**199**		**254**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.1.2 Prasugrel 60/10						
JUMBO (Wiviott)	0	200	0	254		Not estimable
PRINCIPLE (Wiviott)	0	55	0	57		Not estimable
TRITON (O'Donoghue)	62	6813	78	6795	100.0%	0.79 [0.57, 1.10]
Subtotal (95% CI)		**7068**		**7106**	**100.0%**	**0.79 [0.57, 1.10]**
Total events	62		78			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.37 (P = 0.17)						
1.1.3 Prasugrel 60/15						
JUMBO (Wiviott) (1)	2	251	0	254	100.0%	5.06 [0.24, 104.86]
Subtotal (95% CI)		**251**		**254**	**100.0%**	**5.06 [0.24, 104.86]**
Total events	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.05 (P = 0.29)						
1.1.4 Prasugrel all doses						
JUMBO (Wiviott)	2	650	0	254	1.2%	1.96 [0.09, 40.65]
PRINCIPLE (Wiviott)	0	55	0	57		Not estimable
TRITON (O'Donoghue)	62	6813	78	6795	98.8%	0.79 [0.57, 1.10]
Subtotal (95% CI)		**7518**		**7106**	**100.0%**	**0.80 [0.58, 1.11]**
Total events	64		78			
Heterogeneity: Tau² = 0.00; Chi² = 0.34, df = 1 (P = 0.56); I² = 0%						
Test for overall effect: Z = 1.32 (P = 0.19)						

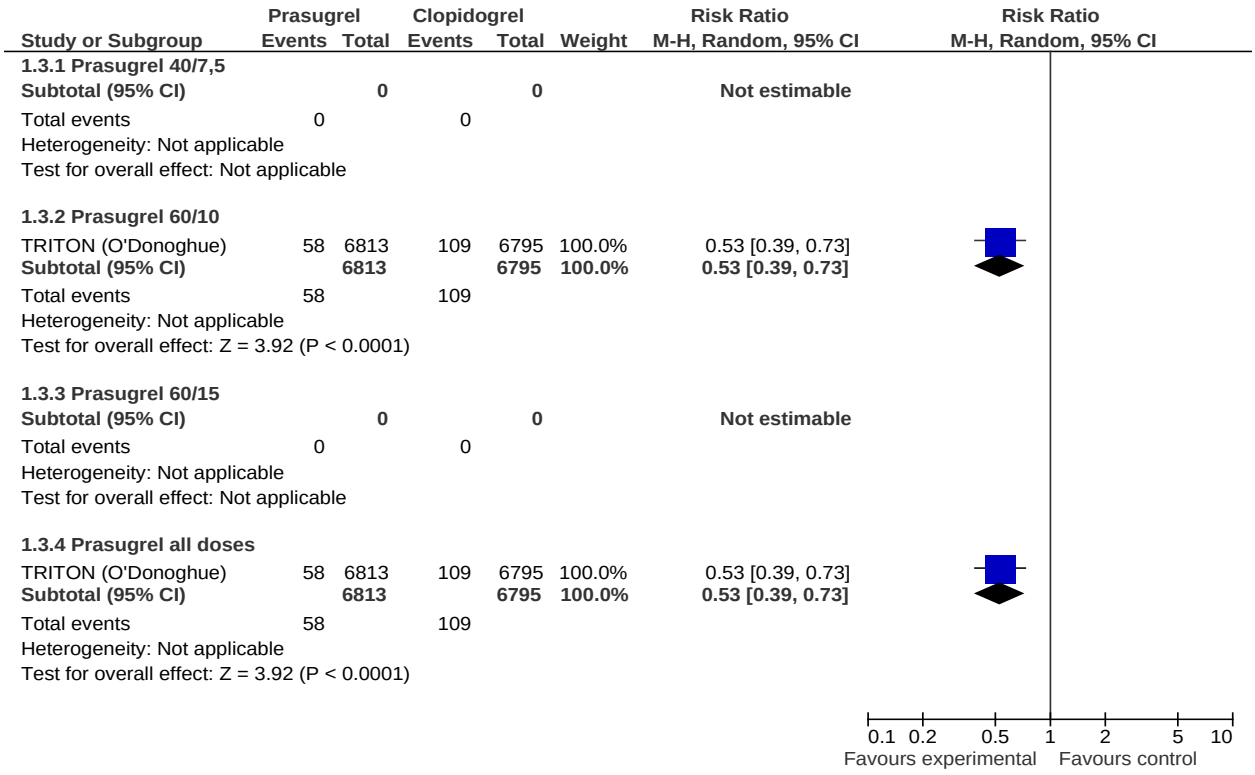


(1) one additonal death not included, unknown cause

AMI short term (14-30 days):

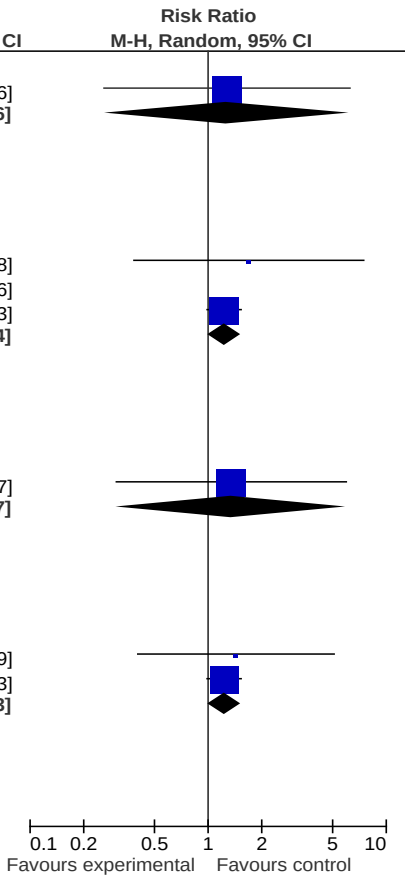


UTVR short term (14-30 days):



Bleeding short term (14-30 days):

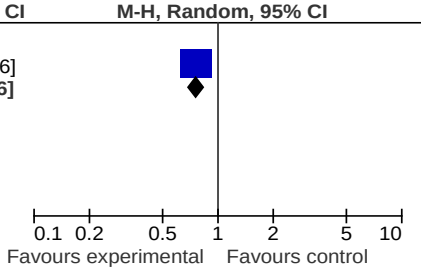
Study or Subgroup	Prasugrel Events	Prasugrel Total	Clopidogrel Events	Clopidogrel Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Prasugrel 40/7,5						
JUMBO (Wiviott)	3	199	3	254	100.0%	1.28 [0.26, 6.26]
Subtotal (95% CI)		**199**		**254**	**100.0%**	**1.28 [0.26, 6.26]**
Total events	3		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.30 (P = 0.76)						
1.4.2 Prasugrel 60/10						
JUMBO (Wiviott)	4	200	3	254	2.1%	1.69 [0.38, 7.48]
SWAP 2010	4	47	6	48	0.0%	0.68 [0.21, 2.26]
TRITON (O'Donoghue) (1)	175	6813	142	6795	97.9%	1.23 [0.99, 1.53]
Subtotal (95% CI)		**7013**		**7049**	**100.0%**	**1.24 [1.00, 1.54]**
Total events	179		145			
Heterogeneity: Tau² = 0.00; Chi² = 0.17, df = 1 (P = 0.68); I² = 0%						
Test for overall effect: Z = 1.93 (P = 0.05)						
1.4.3 Prasugrel 60/15						
JUMBO (Wiviott)	4	251	3	254	100.0%	1.35 [0.31, 5.97]
Subtotal (95% CI)		**251**		**254**	**100.0%**	**1.35 [0.31, 5.97]**
Total events	4		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.39 (P = 0.69)						
1.4.4 Prasugrel all doses						
JUMBO (Wiviott)	11	650	3	254	2.9%	1.43 [0.40, 5.09]
TRITON (O'Donoghue) (2)	175	6813	142	6795	97.1%	1.23 [0.99, 1.53]
Subtotal (95% CI)		**7463**		**7049**	**100.0%**	**1.23 [1.00, 1.53]**
Total events	186		145			
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%						
Test for overall effect: Z = 1.92 (P = 0.06)						



(1) Data from TRITON (O'Donoghue) is recalculated based on % given in publication
(2) Data from TRITON (O'Donoghue) is recalculated based on % given in publication

AMI long term (0-15 months):

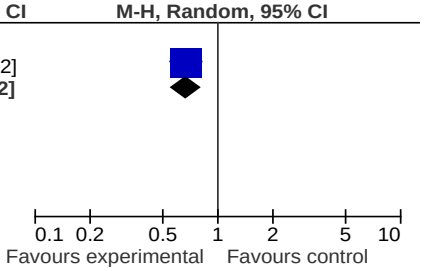
Study or Subgroup	Prasugrel Events	Prasugrel Total	Clopidogrel Events	Clopidogrel Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.2 Prasugrel 60/10						
TRITON (Wiviott) (1)	475	6813	620	6795	100.0%	0.76 [0.68, 0.86]
Subtotal (95% CI)		**6813**		**6795**	**100.0%**	**0.76 [0.68, 0.86]**
Total events	475		620			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.60 (P < 0.00001)						



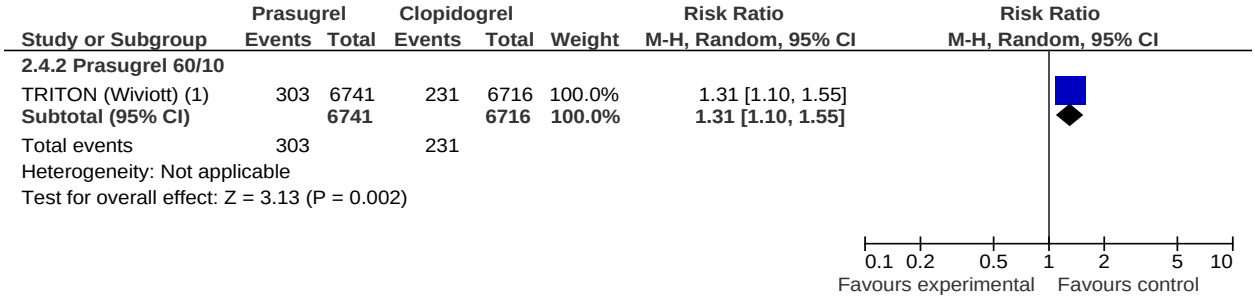
(1) AMI defined in TRITON as Nonfatal AMI

UTVR long term (0-15 months):

Study or Subgroup	Prasugrel Events	Prasugrel Total	Clopidogrel Events	Clopidogrel Total	Weight	Risk Ratio M-H, Random, 95% CI
2.3.2 Prasugrel 60/10						
TRITON (Wiviott)	156	6813	233	6795	100.0%	0.67 [0.55, 0.82]
Subtotal (95% CI)		**6813**		**6795**	**100.0%**	**0.67 [0.55, 0.82]**
Total events	156		233			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.96 (P < 0.0001)						

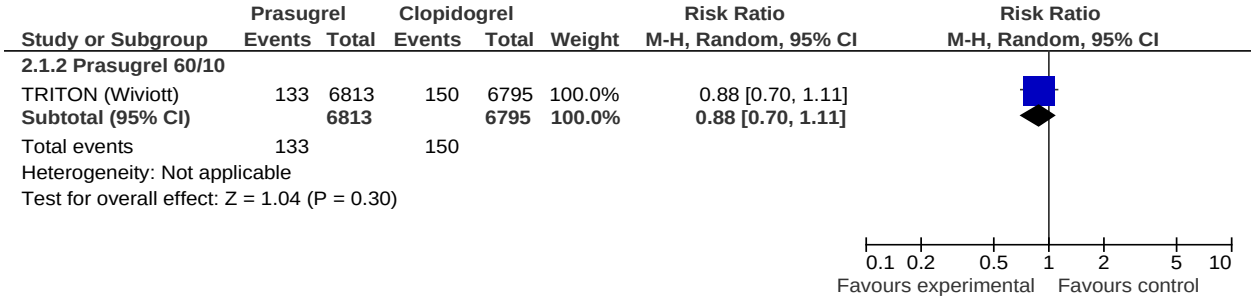


Bleeding long term (0-15 months):

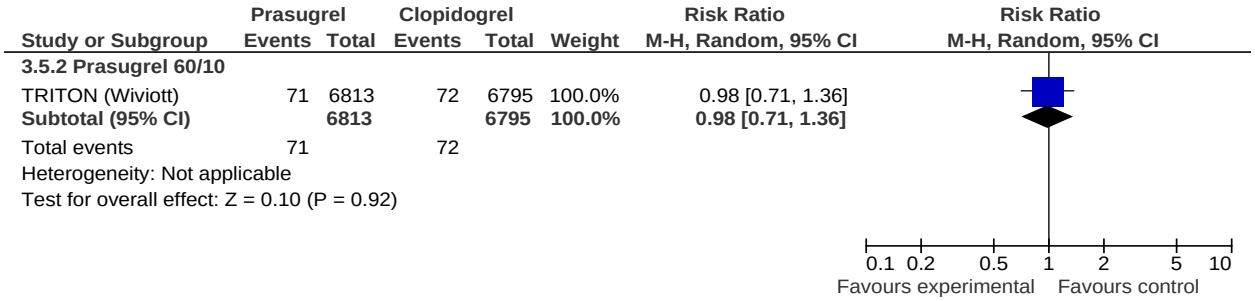


(1) Data for patiens who received >=1 dose of study drug and endpoints occuring within 7 days after study was discontinued or believe

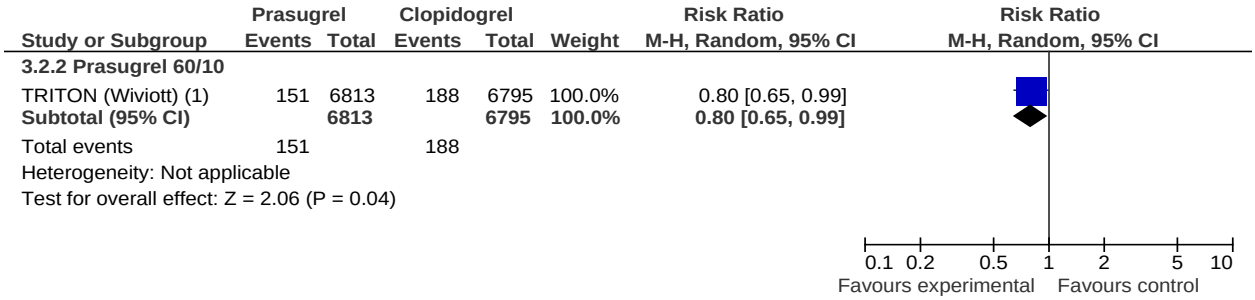
Cardiovascular death long term (0-15 months):



Death long term (1-15 months):



AMI long term (1-15 months):

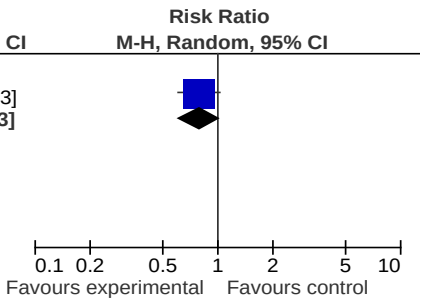


(1) AMI defined in TRITON as Nonfatal AMI

UTVR long term (1-15 months):

Study or Subgroup	Prasugrel Events	Total	Clopidogrel Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.3.2 Prasugrel 60/10						
TRITON (Wiviott)	98	6813	124	6795	100.0%	0.79 [0.61, 1.03]
Subtotal (95% CI)		**6813**		**6795**	**100.0%**	**0.79 [0.61, 1.03]**
Total events	98		124			

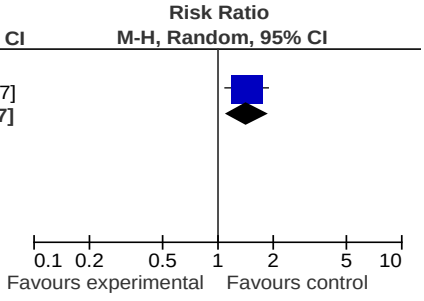
Heterogeneity: Not applicable
Test for overall effect: Z = 1.77 (P = 0.08)



Bleeding long term (1-15 months):

Study or Subgroup	Prasugrel Events	Total	Clopidogrel Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.4.2 Prasugrel 60/10						
TRITON (Wiviott) (1)	128	6741	89	6716	100.0%	1.43 [1.10, 1.87]
Subtotal (95% CI)		**6741**		**6716**	**100.0%**	**1.43 [1.10, 1.87]**
Total events	128		89			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.63 (P = 0.009)



(1) Data for patiens who received >=1 dose of study drug and endpoints occuring within 7 days after study was discontinued or believe

APPENDIX 3: GRADE TABLES

Short term

prasugrel compared to clopidogrel for patients undergoing PCI

Patient or population: patients undergoing PCI

Settings: short term 14- 30 days

Intervention: prasugrel

Comparison: clopidogrel

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk clopidogrel	Corresponding risk prasugrel			
death -cardiovascular, short term 14-30d Follow-up: 14-30 days	**11 per 1000**	**9 per 1000** (6 to 12)	**RR 0.79** (0.57 to 1.10)	14174 (3 studies)	**low**[1,2,3]
AMI - short term 30d Follow-up: 30 days	**64 per 1000**	**48 per 1000** (42 to 55)	**RR 0.75** (0.65 to 0.86)	14062 (2 studies)	**high**
UTVR - short term 30d Follow-up: 30 days	**16 per 1000**	**8 per 1000** (6 to 12)	**RR 0.53** (0.39 to 0.73)	13608 (1 study)	**low**[2,4]
TIMI major or minor bleeding - short term 30d Follow-up: 30 days	**21 per 1000**	**26 per 1000** (21 to 32)	**RR 1.24** (1.0 to 1.54)	14062 (2 studies)	**high**[5,6]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

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

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

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

Very low quality: We are very uncertain about the estimate.

[1] Not enough studies with events to conclude on inconsistency

[2] Total number of events is less than 300 (a threshold rule-of-thumb value) (based on: Mueller et al. Ann Intern Med. 2007;146:878-881 <http://www.annals.org/cgi/content/abstract/146/12/878>)

[3] 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect includes both 1) no effect and 2) appreciable benefit or appreciable harm.

[4] Only one study. Reproducability unknown.

[5] Data from one of the studies is recalculated based on % given in publication. Chose not to downgrade.

[6] 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect includes both 1) no effect and 2) appreciable benefit or appreciable harm. Borderline. Chose not to downgrade.

Long term

prasugrel compared to clopidogrel for patients undergoing PCI

Patient or population: patients undergoing PCI

Settings: long term - 15 months

Intervention: prasugrel

Comparison: clopidogrel

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk **clopidogrel**	Corresponding risk **prasugrel**			
death - cardiovascular - long term 15m Follow-up: 15 months	**22 per 1000**	**19 per 1000** (15 to 24)	**RR 0.88** (0.70 to 1.11)	13608 (1 study)	**moderate**[1]
AMI - long term 15m Follow-up: 15 months	**91 per 1000**	**69 per 1000** (62 to 78)	**RR 0.76** (0.68 to 0.86)	13608 (1 study)	**moderate**[1]
UTVR - long term 15m Follow-up: 15 months	**34 per 1000**	**23 per 1000** (19 to 28)	**RR 0.67** (0.55 to 0.82)	13608 (1 study)	**moderate**[1]
TIMI major or minor bleeing - long term 15m Follow-up: 15 months	**34 per 1000**	**45 per 1000** (37 to 53)	**RR 1.31** (1.1 to 1.55)	13457 (1 study)	**low**[1,2]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its

95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

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

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

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

Very low quality: We are very uncertain about the estimate.

[1] Not enough studies to conclude on inconsistency

[2] Data on bleeding only reported for those who got one dose or more of study drug. 151 patients less than used in efficacy calculations.

APPENDIX 4: EXCLUDED STUDIES

First author	Year of publication	Name of study	Reason for exclusion
Anonymous (28)	2007	TRITON-TIMI 38	Abstract
Anonymous (29)	2009		Review
Antman (30)	2008	TRITON-TIMI 38	Re-analysis of TRITON-TIMI 38
Capranzano (31)	2009		Review
Cowley (32)	2009		Review
Floyd (33)	2009	TRITON-TIMI 38	Sub-group from TRITON-TIMI 38
Khoynezhad (34)	2009		Review
Mahoney (24)	2010	TRITON-TIMI 38	Economic evaluation
Mariani (35)	2009		Review
Montalescot (27)	2009		Sub-group from TRITON-TIMI 38
Montalescot (36)	2010	ACAPULCO	Less than half got PCI
Morrow (37)	2009	TRITON-TIMI 38	No exact numbers
Murphy (38)	2008		Secondary events
O'Donoghue (39)	2009		Wrong comparator
Pride (40)	2009	TRITON-TIMI 38	Selected subgroup
Schafer (41)	2009		Summary of TRITON-TIMI 38
Serebruany (42)	2008		Review
Serebruany (43)	2008		Review
Spinler (44)	2009		Review
Veverka (45)	2009		Review
Webster (46)	2009		Comment
Wiviott (47)	2006	TRITON-TIMI 38	Design
Wiviott (26)	2008	TRITON-TIMI 38	Sub-group from TRITON-TIMI 38
Wiviott (48)	2008	TRITON-TIMI 38	Re-analysis of TRITON-TIMI 38 with only composite endpoints
Wiviott (49)	2008	TRITON-TIMI 38	Sub-group from TRITON-TIMI 38