Executive Summary

◆ Percutaneous coronary angioplasty (PCI) is the dominant therapy for treating flow limiting coronary lesions
◆ Stents prevent early vessel closure and reduce need for repeat procedure and are the standard of care for PCI
◆ Stent thrombosis is platelet centric
◆ Dual anti-platelet therapy (aspirin and clopidogrel) given as a 600mg bolus 24 hours pre-PCI and 75 mg od has become the established therapeutic management
◆ Drug eluting stents significantly reduce the need for a repeat procedure compared to bare metal stents
◆ Drug eluting stents limit the re formation of protective endothelium and thus introduce the potential for later stent thrombosis
◆ Stent thrombosis probably occurs in 1-2% of patients but is associated with up to a 50% death and MI rate (note ~ 3 million stents placed worldwide pa)
◆ Concerns regarding the safety of DES (stent thrombosis) have been extensively studied
◆ Most stent thrombosis occurs early (within 6 months)
◆ The mechanism for early stent thrombosis is easier to understand than late and very late stent thrombosis
◆ The most potent factor for stent thrombosis is discontinuation of clopidogrel
  Long term dual anti-platelet therapy is associated with bleeding
◆ Certain groups such as those presenting to PCI early with a pro-thrombotic milieu may need improved and more potent anti-platelet therapy
◆ Patients vary in their response to clopidogrel – some may, through uncertain mechanisms be under-treated
◆ Newer agents such Prasugrel appear to be more potent and thus may have a role in PCI especially in some sub groups
◆ Comparisons with standard care (pre loading with clopidogrel) have been criticised
1.0 Background

1.1 Percutaneous coronary intervention & Platelet Activity

Percutaneous coronary intervention (PCI) is the dominant revascularisation therapy with an increasing ratio of 4 PCIs for every coronary artery bypass graft in the UK, and with ratios in some parts of Europe reaching 8 PCIs for each CABG undertaken. The rapid expansion of PCI relates to a number of factors including reduced procedural invasiveness, short hospital stay and good symptomatic outcome, together with prognostic benefit in some subgroups, such as those with acute coronary syndromes. This expansion coincides with the multiple parallel developments of improved training, increased technological development, a wealth of interventional trials and registries, an understanding of the critical role of stenting, appropriate use of drug eluting stents but perhaps most important of all, in safety terms, the increased research and subsequent understanding of the important role of adjunctive pharmacotherapy.

Percutaneous coronary angioplasty induces significant vessel wall trauma as part of the process of reducing the flow limitation associated with fixed obstructive atheromatous disease. Histopathology indicates that following balloon inflation circumferential and longitudinal dissection planes are produced. Not only does such injury expose sub-endothelial pro-coagulant vessel wall constituents (cholesterol crystals, fibroblasts, calcium, degenerated red blood cells and tissue factor) to flowing blood but any thrombo-protective endothelium (which normally contains anti-thrombotic and anti-restenotic constituents such as heparans, nitric oxide and Prostacyclin PGI2) is removed as a result of the balloon injury. Many of these events are potent stimulants to platelet activation and aggregation. Clearly following PCI, platelet initiated and platelet-mediated thrombus becomes an important potential risk to vessel patency. Balloon angioplasty alone also carries the further risk of acute vessel closure since the innermost vessel wall layer, the intima is disrupted and this disrupted layer can (and did) physically obstruct the vessel, causing acute occlusion requiring urgent coronary bypass surgery. The evolution of coronary stents fixed the intimal disruption and their introduction in the early–mid 1990s dramatically reduced the need for urgent coronary surgery which has now become a rare event, hence allowing for PCI (with stenting) to be undertaken in sites without coronary artery by-pass grafting facilities. However the 2 main consequences of vessel injury and pro-thrombotic inflammatory response induced by PCI with stent implantation are potentially:

1. Platelet-mediated vessel (stent) occlusion
2. Early myocardial injury detectable by biomarkers such as CK-MB or troponins which is also partially due to platelet activity

These are the two mechanisms that a new antiplatelet therapy would be expected to address with greater efficacy than the current standard of aspirin and clopidogrel.

At the time of coronary stent introduction anti-thrombotic therapy consisted of a combination of aspirin and warfarin, as it had been for balloon angioplasty. However despite this regimen stent thrombosis (ST) became a significant clinical issue with rates of 10-20% (depending on the stent). Stent thrombosis is an acute event- patients may be discharged well from hospital well, and then suffer acute ST or late ST, resulting in acute vessel closure, which has been reported to be associated with up to 50% incidence of acute myocardial infarction or death. Not only was the high rate of ST
not attenuated by the combination of aspirin and warfarin but attainment of therapeutic INR warfarin took several days to complete and femoral artery complication rates were high (up to 15% significant local haematoma formation). For example, at Glenfield Hospital in Leicester in 1996 the median in-patient stay post stenting was 6.6 days and the assess site complication rate 12%.

1.2 PCI and Anti-thrombotic Therapy: Evolution

1.2.1 Aspirin & warfarin

Improvements in the understanding of the mechanisms of ST led to the notion that since post stent arterial thrombosis was likely to be platelet-centric then maybe more potent anti-platelet therapies would be a better prophylactic regimen than just aspirin with warfarin. With the established knowledge that activation, adhesion and aggregation of platelets play a central role in the propagation of intracoronary thrombi, optimal antiplatelet therapy became fundamentally important in the management of several manifestations of cardiovascular disease including stent thrombosis. Over the two decades of the 80s and 90s aspirin had become the cornerstone of antiplatelet therapy (1, 2). Aspirin inhibits cyclooxygenase by its irreversible acetylation thereby preventing the formation of thromboxane A2 (TxA2). TxA2 plays an important role as one of the agonists in the induction of platelet aggregation and vasoconstriction. Landmark trials had established the efficacy of aspirin in the prevention of recurrent atherothrombotic vascular disease and have also shown that it reduces the frequency of ischaemic complications after PCI.[ 3-6). Despite the proven benefits of aspirin a significant proportion of patients continued to suffer major adverse cardiac events (MACE) whilst on therapy. One explanation for this is that aspirin is a relatively weak inhibitor of overall platelet activation; specifically, it inhibits essentially only the arachidonic acid pathway and therefore platelet activation can still occur via the P2Y12 receptor, and through activation of platelets receptors by high concentrations of thrombin and collagen, both of which are present in the local environment following balloon and stent injury of vessel wall. While TxA2 has agonistic influence on the P2Y12 receptor, preventing the formation of TxA2 does not prevent the activation of platelets in the setting of vessel wall damage. Since platelets are activated in such circumstances, and go on to propagate thrombus formation, and since anti-coagulants such as warfarin not only are of no value but indeed add to the problem through bleeding, stenting seemed destined for being of limited benefit against the background of excess adverse risk.

It became a logical assumption however that two antiplatelet drugs in combination may be a superior strategy to combat thrombotic complications of PCI (ie enzyme release and ST) than aspirin and warfarin. The thienopyridine, ticlopidine, was already being used in the secondary prevention of stroke. (7). A small randomised trial suggested that both (IVUS guided) good stent deployment and the use of additional anti-platelet therapy could indeed lead to lower stent thrombosis rates (8)

1.2.2 Aspirin and Ticlopidine

Ticlopidine and aspirin became the standard of care post stenting. The use of ticlopidine use was “off-licence” but its uptake had a dramatic impact on reducing stent thrombosis rates. However, ticlopidine was expensive and had a poor side effect profile – agranulocytosis and even aplastic
anaemia (albeit reversible) were not uncommon. Both ticlopidine and its successor, clopidogrel are rapidly absorbed prodrugs that are modified by the liver into their active metabolites. They exert their action by irreversibly inhibiting adenosine diphosphate binding to the P2Y$_{12}$ receptor on the platelet surface. By blocking this receptor they interfere with platelet activation, degranulation, and aggregation. Neither drug has important effects on arachidonic acid metabolism, and as such exert their main influence on a completely separate but important portion of the platelet aggregatory pathway.

In a meta analysis by Metha (9) it was reported that in randomized trials of aspirin plus thienopyridines in patients undergoing intracoronary stenting, there was demonstrated a marked benefit of aspirin plus ticlopidine in reducing death or myocardial infarction compared with aspirin alone (OR 0.23, 95% CI 0.11-0.49, P=0.0001) or aspirin plus warfarin (OR 0.51, 95% CI 0.33-0.78, P=0.002).

1.2.3 Aspirin and clopidogrel: current standard of care

It has been clearly shown that clopidogrel with aspirin has equal if not better efficacy outcomes and less side effects than ticlopidine and aspirin (10,11). Thus, in a meta-analysis by Bertrand (12), of 13,955 patients, the pooled rate of major adverse cardiac events was 2.1% in the clopidogrel group and 4.0% in the ticlopidine group. After adjustment for heterogeneity in the trials, the odds ratio (OR) of having an ischemic event with clopidogrel, as compared with ticlopidine, was 0.72 (95% confidence interval [CI] 0.59 to 0.89, p = 0.002). Mortality was also lower in the clopidogrel group compared with the ticlopidine group-0.48% versus 1.09% (OR 0.55, 95% CI 0.37 to 0.82; p = 0.003). For these reasons clopidogrel has largely superseded ticlopidine as the first choice thienopyridine. Landmark trials have established an undoubted benefit of clopidogrel alone or in combination with aspirin in the context of arteriosclerotic vascular disease, acute coronary syndromes and prolonged dual antiplatelet therapy following PCI. In particular important trials showed that dual anti-platelet therapy was better than warfarin treatment (13,14,15).

As a result dual antiplatelet therapy with aspirin and clopidogrel became the evidenced based standard for all patients undergoing PCI (16 17 18 19).

The CURE trial was an important study published in the NEJM in 2001 (20) which further established a number of principles regarding dual anti-platelet therapy:

(1) in patients with acute coronary syndromes longer term (including those undergoing PCI in the context of ACS) 12 month dual anti-platelet therapy including clopidogrel resulted in lower event rates than with aspirin and placebo. In 12,562 randomly assigned patients presenting within 24 hours after the onset of symptoms to receive either clopidogrel (300 mg immediately, followed by 75 mg once daily) (6259 patients) or placebo (6303 patients) in addition to aspirin for 3 to 12 months the first primary outcome- a composite of death from cardiovascular causes, nonfatal myocardial infarction, or stroke - occurred in 9.3 percent of those in the clopidogrel group and 11.4 percent in the placebo group (relative risk with clopidogrel as compared with placebo, 0.80; 95 percent confidence interval, 0.72 to 0.90; P<0.001). The second primary outcome (the first primary outcome or refractory ischemia) occurred in 16.5 percent of those in the clopidogrel group and 18.8 percent of the patients receiving placebo (relative risk, 0.86, P<0.001). The percentages of patients with in-
hospital refractory or severe ischaemia, heart failure, and revascularization procedures were also significantly lower with clopidogrel.

But:

(2) Dual anti-platelet therapy carries a risk of excess bleeding. There were significantly more patients with major bleeding in the clopidogrel group than in the placebo group (3.7 percent vs. 2.7 percent; relative risk, 1.38; P=0.001), but there were not significantly more patients with episodes of life-threatening bleeding (2.1 percent vs. 1.8 percent, P=0.13) or hemorrhagic strokes. Much of the excess bleeding was dependant on the concomitant aspirin dosage.

Furthermore:

(3) **Pre-treatment** with clopidogrel appeared to be beneficial since the patients were randomised on admission and therefore received active or placebo prior to their PCI intervention clopidogrel. The results of PCI-CURE were subsequently published as a sub-study (21). Of the 2658 patients with non-ST-elevation acute coronary syndrome undergoing PCI in the CURE study pre-treatment with aspirin and study drug was for a median of 6 days before PCI during the initial hospital admission, and for a median of 10 days overall. After PCI, most patients (>80%) in both groups received open-label thienopyridine for about 4 weeks, after which study drug was restarted for a mean of 8 months. The primary endpoint, a composite of cardiovascular death, myocardial infarction, or urgent target-vessel revascularisation within 30 days of PCI was reached in 59 (4.5%) patients in the clopidogrel group, compared with 86 (6.4%) in the placebo group (relative risk 0.70 [95% CI 0.50-0.97], p=0.03). Long-term administration of clopidogrel after PCI was associated with a lower rate of cardiovascular death, myocardial infarction, or any revascularisation (p=0.03), and of cardiovascular death or myocardial infarction (p=0.047). Overall (including events before and after PCI) there was a 31% reduction cardiovascular death or myocardial infarction (p=0.002). Because the patients randomised to the active arm had received active treatment between admission and PCI and then both groups (active and placebo) had received clopidogrel for a month, this sub-study established the principle of pre-treatment(pre-PCI loading), which was supported by a further trial sub-group analysis (of the CREDO study) which also addressed its potential timing (> 6 hours pre) (22). Further studies have explored the timing and dose of pre-PCI loading with clopidogrel- in general terms it is felt that based on all data available that for optimal benefit 600 mg should be given for > 24 hours pre-procedure (23).

While the Albion study (24) suggested that in laboratory studies 900 mg of clopidogrel had better outcomes (a significant dose-response was observed for the vasodilator-stimulated phosphoprotein index, a measure of P2Y(12) receptor inhibition) this was not supported by clinical data which reported found no benefit of 900mg clopidogrel over 600 mg (25).

The standard of care now for both those presenting with acute coronary syndrome, in whom PCI is mandated as part of European and US Guideline protocols, and those going for planned PCI should, based on the data, be pre-load with 300-600 mg clopidogrel for > 24 hours pre –procedure.
1.3 Bare metal versus drug-eluting stents and antiplatelet therapy.

With the use of clopidogrel and aspirin stent thrombosis rates fell to approximately 2%. However, the main therapeutic weakness of bare metal stents, in-stent restenosis, (ISR), became the focus of research attention. Bare metal stents (BMS) are associated with a need for a repeat PCI (target lesion revascularisation) in up to 10-20% of patients because of restenosis within the stent, a process based on the over-healing response of smooth muscle cells to injury. It is this over-proliferation of smooth muscle cells that leads to the need for excess repeat intervention usually within 6-9 months of first procedure due to scar tissue deposition within the stent (neointima). Drug eluting stents inhibit this over healing smooth muscle cell response an reduce the need for a repeat procedure by up to 70%. DES are stents covered by polymer into which has been absorbed locally effective concentrations of drugs that inhibit the inflammatory healing response induced by the trauma associated with stent implantation and thereby attenuate the formation of neointima. In essence these compounds fall into two groups – (a) sirolimus - an anti-inflammatory compound discovered by Ayest in the Easter Islands in 1968 and initially used systemically to limit renal transplant rejection or its derivatives, evolrolimus and zotarolimus or (b) Paclitaxel - an inhibitor of mitosis known since Roman times. Multiple randomised trials, as well prospective and retrospective observational and “real life” registry studies have repeatedly shown that patients receiving stents delivering such compounds have up to a 70% reduction in need for repeat PCI through inhibition of the restenotic process. (26-43)

Following a NICE review (January 2008) DES have become the recommended standard of care in those patients especially in those at higher risk for repeat intervention (44). In particular those lesions with small reference diameters (<3.0mm) and longer length (>15mm) were deemed appropriate for treatment with DES. In general approximately 50-75 % of patients undergoing PCI will receive a DES depending on local case mix. While DES dramatically reduce the need for repeat intervention there have been raised safety concerns. Part of these revolve around the bystander concept: the rate of beneficial/protective endothelial regeneration is reduced by the drug, hence delaying endothelialisation of the stent surface which is an important part of reducing the risk of ST since the endothelium protects the pro-thrombogenic stent strut and disrupted intima from the platelets. Normally with bare metal stents endothelial recovery takes approximately a month – while the exact time for the endothelial cells to fully recover function after DES is unclear, periods of up to and beyond a year have been suggested (45-48).

Some have proposed that in addition (49) it is the polymer that may lead to delayed healing furthermore a prolonged inflammatory response: indeed a study by van Giessen some years ago showed that certain polymers may be very pro-inflammatory (50). Many of the current polymers have been shown through fibrin marker studies to be much less inflammatory and most now are bioneutral. Irrespective, by mid 2006 there were concerns expressed that DES had a higher ST rate than bare metal stents and irrespective of the mechanism that this may lead to excess clinical adverse events, since ST out of hospital could lead to a risk death or myocardial infarction in up to 50% in those suffering it (51).
2.0  **Stent thrombosis in the clopidogrel era**

2.1  **Why is there concern about ST?**

Concerns relating to the potentially high rates of ST and the clinical consequences in patients treated with DES have escalated over the last few years and this has been reflected in media scrutiny as well as patient and commissioner anxiety, but bears objective analysis because it is directly relevant to the current appraisal.

In 2004 McFadden reported four cases of stent thrombosis (two CYPHER, two TAXUS) all occurring between 300 and 450 days after stent implantation and all presenting soon after both aspirin and clopidogrel therapy were stopped (52)

In 2006 at the European Society of Cardiology, Camenzind and colleagues claimed there was a significant association between the use of DES and excess mortality– an absolute 3.9% difference for the CYPHER stent. Interestingly, this presentation has never been published as a full peer review paper, but it did raise serious concerns and caused a dramatic reduction in the use of DES, to <50% in the UK in 2007 and to even lower usage in other countries (e.g a fall from 60% to 10% in Sweden for example).

2.2  **Causes**

A recent very large registry lends strong support to many of the concepts that have evolved regarding the causes of ST that are outlined below. In this study published in the Journal of the American College of Cardiology in April 2009 (53) Van Werkum and colleagues suggest, as has been done previously that discontinuation of clopidogrel and stent under-sizing were the most significant predictors of ST out of an extensive list of clinical, procedural, and angiographic predictors. Of 19,840 patients followed to nearly 3 years 437 (2.2%) presented with ST. Of these 73% were within 30 days (32% within 24 hours (acute)) 13% were between 30 days and a year and 13% presented >1 year. BMS ST was 2.2% and DES ST 2.0%. Compared to those who did not have ST independent predictors of ST (in hierarchal order) were

1.  Cessation of clopidogrel (at various time points but highest risk within 30 days)
2.  Stent under-sizing
3.  Current malignancy
4.  Intermediate CAD (≥50% stenosis) proximal to the culprit lesion
5.  Suboptimal procedural result (TIMI flow grade <3 after PCI)
6.  Uncovered dissection
7.  Bifurcation stenting
8.  LVEF <30%
9.  PAD
10. Intermediate CAD distal to the culprit lesion

11. **No aspirin therapy**
12. Any DES use
13. Diabetes
14. Younger age (protective)
Many of these factors have been previously recognised.

The interesting aspect of this registry study is that it confirms that the ST issue is essentially an event 50% of the incidence of which appears to occur early and may thus be contributed to through technical (technique/procedural) issues, but is also related to the thrombogenicity of the lesion. For patients who underwent elective PCI for stable angina, the cumulative rate of stent thrombosis was 1%, while for those who were stented for unstable angina/NSTEMI the rate was 1.8%, and rose to 4.3% for those with STEMI. The timing of stent thrombosis was significantly different for the different categories of patients: 79% of stent thromboses in STEMI patients occurred early (within 30 days) vs. 65% in NSTEMI and stable angina patients. On the other hand, the proportion of late and very late (beyond 30 days) stent thrombosis was higher in the stable angina and NSTEMI groups.

- As has been shown before lack of clopidogrel was mostly a factor early after stenting. Others (Colombo) have shown that discontinuation of clopidogrel was a factor for ST within the first 6 months, whereas in this registry it was an important factor within the first 30 days (HR 36.5, 95% CI 8.0-167.8).
- The data also suggests that potent, continuous DAPT is required for at least 6 months. In this registry discontinuation of therapy between 30 days and 60 days and after 6 months from the index procedure likewise predicted stent thrombosis, (HR 4.6, 95% CI 1.4-15.3, and HR 5.9, 95% CI 1.7-19.8, respectively). Thereafter while important, less ST occurs and other factors (as yet unknown may come into play).
- It should be particularly noted that with early ST technical (good procedure) issues are likely to be paramount. In this study in particular under-sizing of stent appears to be an issue.
- In many ways potent DAPT given early is protecting somewhat against less than optimal stenting (for operator, lesion or stent conformability reasons) in the setting of this being the time when thrombogenic factors (due to vessel wall disruption) are most potent.

What the study doesn’t tell us is which patients with DES suffer late ST since it would only be these who we would want to give longer term (> 1 year up to 4 years DAPT)

**Higher risk lesions**

- Other data suggests that STEMI patients are at no greater risk with DES - stent thrombosis was not seen in any of the 186 Sirolimus patients compared to 1.6% in those in the bare metal arm (RESEARCH AMI registry) (54).
- See Dutch Registry above
- In general the pro-thrombotic milieu of a STEMI or NSTEMI may present more of a challenge to stenting, especially in the first few days but this is not impacted by the stent choice
Precipitating factors

- Certain factors predict stent thrombosis, including stent under-expansion and residual reference diameter (55), supporting the concept that DES-use is not an excuse for inadequate technique.

- Most importantly in repeated publications discontinuation of anti-platelet therapy is the most powerful predictor of stent thrombosis

- Inadequate protection against platelet activation (responsiveness see below) especially early may be important

In general, predictors of ST can be classified into three groups:

1. Those related to the patient:
   - Diabetes mellitus, renal failure, low LVEF, clinical setting (ACS at presentation), antiplatelet therapy discontinuation, antiplatelet therapy resistance (potency need)

2. Those linked to the treated lesion:
   - Lesion length and diameter, pre-procedural MLD and stenosis percentage, Type C lesion, Bifurcation

3. Those associated with the PCI procedure
   - Stent length, maximal balloon diameter, post-procedural MLD and residual stenosis percentage, number of stent per lesion, stent under-expansion or mal-apposition, residual thrombus, residual dissection.

2.2 Factors to take into account in the analysis of ST

Concerns related to an excess of late stent thrombosis with DES following the ESC presentation in 2006, and its associated adverse clinical outcomes, resulted in a number of changes in the thinking about stent thrombosis and DES safety. Such considerations have particular relevance to this Prasugrel NICE review.

These can be summarised as :-

- The Academic Research Consortium (ARC) based in Boston set about defining both stent thrombosis and its timing. This was vital because at that time there were no previously agreed standards for deriving a realistic assessment of the rate of ST in large study groups.
- A significant research effort was initiated on a number of fronts including review of all the previous randomised controlled clinical trials at patient level data (Camazind had derived his presented abstract findings from the published data). All previous registry data bases were re-analysed along the lines of the new ARC definitions and these and meta-analyses were published.
- On and off label use of DES and the outcomes were compared
• New RCT were initiated (e.g. The PROTECT Trial – CYPHER versus ENDEAVOR in 8,800 patients with ARC defined ST as the 3 year primary end point. Due to report 2010)
• The FDA published a position statement indicating all patients with DES should be given dual anti-platelet therapy (DAPT) for one year, and the British Cardiovascular Society followed suit
• Subsequently a review of the bleeding risk associated with prolonged DAPT was published as data sub-sets from previous studies
• Considerations regarding the length of required time for DAPT have need to be revisited.
• Limitations of clopidogrel use were re-examined, and in particular the vexed question of “clopidogrel resistance”. The response of individuals to clopidogrel therapy is heterogeneous and a low response leaves those patients with correspondingly more reactive platelets, hence rendering them at risk of ST. No assessment of individual response to clopidogrel is made in routine clinical practice - all patients are treated with standard doses even though we know that they respond differently (see below)
• The improvement in our understanding of the timing of events has become particularly important. Thus, early stent thrombosis is often due to inadequate apposition of the stent to the vessel wall or inadequate anti-platelet protection during early higher risk first few days, whilst late and very late ST are more difficult to explain (and may relate to factors such as poor individual responses to clopidogrel or delayed endothelialisation or late malaposition where the vessel wall “grows away from the stent). Late or very late stent thrombosis may well require longer DAP therapy.
• Newer agents and for the purpose of this review, Prasugrel, now have available published data and the relevance of this to the UK population and whether it has a role in improving outcomes in patients undergoing PIC compared to clopidogrel are important considerations.

2.2.1 How do we define ST?

The Academic Research Consortium (ARC) published recently (56) the definition of stent thrombosis and categorized this according to the timing of ST. ST is considered as being “acute” when it has occurred between 0 and 24 h after stent implantation, “subacute” between 24 h and 30 days, “late” between 30 days and 1 year, and “very late” after 1 year. Acute and subacute ST are sometimes replaced with the term “early” ST.

**Definite ST** is defined as when there is angiographic confirmation of ST (the presence of a thrombotic occlusion –that originates in the stent or in the segment 5mm proximal or distal to the stent) together with the presence of at least one of the following criteria within a 48-hour window: (i) acute onset of ischemic symptoms at rest, (ii) new ischemic electrocardiographic changes that suggest acute ischemia or (iii) a typical rise and fall in cardiac biomarkers; (iv) in the presence of a pathological confirmation of ST (evidence or recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy). The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed ST (silent occlusion).

**Probable ST** is defined as the presence of any unexplained death within the first 30 days after stent implantation, or in the presence of any MI related to documented acute ischemia in the territory of
the implanted stent, without necessary angiographic confirmation of ST and in the absence of any other obvious cause, irrespective of the time after the index procedure.

**Possible ST** is defined as any unexplained death from 30 days after PCI until the end of follow-up.

### 2.2.1 Is stent thrombosis more common with DES compared to BMS?

In addition to the Dutch registry above there is significant data addressing this issue including RT, prospective and retrospective registry, observational studies and meta-analyses.

- **Incidence of ST with BMS**

  Early definite ST was a common complication following BMS implantation in the early 1990s with an incidence ranging from 10 – 15 %. Treatment with dual antiplatelet therapy (aspirin and thienopyridine) for four weeks after placement of BMS has reduced this risk to less than 2%. A review of 6058 patients with BMS indicates that ST rate was 1.6% (57). The timing of ST was acute in 11%, subacute in 64% and late in 25% of the patients. Importantly in the context of worries about DES delayed re-endothelialisation and its impact on late stent thrombosis, 8/24 patients suffered stent thrombosis beyond 6 months. Overall outcome was poor; 6 month major adverse clinical events comprised death (11%), re-infarction (16%), and recurrent stent thrombosis (12%) Few data are available on the rate of very late stent thrombosis after BMS implantation although there is a report of 0.2% in a large meta-analysis of 38 trials (58).

- **Incidence of ST : BMS vs DES**

  To determine the incidence of ST in patients treated with BMS versus DES several meta-analyses have been performed in the past few years. (Note: SES = sirolimus-eluting stent; PES = paclitaxel-eluting stent)

  - To date, the largest meta-analysis study has been published by Stetteler and colleagues (58). This included 38 trials (18023 patients) and compared SES (6771 patients) vs PES (6331 patients) vs BMS (4921 patients) with a 4 years follow-up. **The study concluded that there was no significant difference in the risk of ST in the overall follow-up period.** However, the risk of late definite ST increased with PES (HR 2.11, p=0.017 vs BMS and 1.85, p=0.041 vs SES). **Nevertheless, this outcome did not impact on mortality.**

  - A meta-analysis of 14 trials including data from 4958 patients compared SES versus BMS. This included acute MI cases in 24% of patients, some chronic total occlusions, bypass grafts and other complex lesions. The clinical outcome was all-cause mortality and the follow-up for for 1 – 4.9 years. **In this study there was no significant difference in the overall risk of ST between DES and BMS. However, there was a slight increase in the risk of ST associated with SES after the first year. ST was defined as per study protocols and was observed in 65 patients (34 with SES and 31 with BMS). After the first year, ST occurred in nine patients, eight of whom had received SES. Over the 4-year follow up period following the first year after the procedure, the overall risk for ST was 0.6% in the SES group and 0.05% in the BMS group (59).
Stone et al (60) analysed safety and efficacy as the major clinical end points in a pooled patient-level analysis from four double-blind trials in which 1748 patients were treated with either SES or BMS and five double-blind trials in which 3513 patients were treated with either PES or BMS (TAXUS I, II, IV, V and VI). The follow-up was up to 4 years and the selected patients were clinically stable and had simple native lesions. The 4-year rates of ST were 1.2% in the SES vs 0.6% in the BMS-group (p=0.20) and 1.3% in the PES vs 0.9% in the BMS group (p=0.30). However, after 1 year, there were five episodes of ST in patients with SES vs none in patients with BMS (p=0.025) and nine episodes in patients with PES vs two in patients with BMS (p=0.028). The number of episodes of ST within the first year was identical among patients treated with SES, PES or BMS. Again, the rates of death or MI did not differ significantly between the groups.

Using a hierarchical classification of ST as set by the ARC, Mauri L et al (61) analyzed 878 patients treated with SES, 1400 treated with paclitaxel-eluting stents (PES) and 2267 treated with BMS. Four year follow-up data in clinically stable patients with simple native lesions were pooled and analysed for ST as primary outcome. The incidence of early, late or very late ST did not differ significantly between patients with DES and those with BMS in these randomized clinical trials, although the power to detect small differences was limited. Outcome in the 68 patients with definite or probable ST was poor, 21 patients died (30.9%) and 57 had MI (83.8%). Outcome rates after ST were similar among treatment groups. At 4 years, the proportion of deaths from ST were 7.0% in the SES vs 11.1% in the corresponding BMS group and 8.2% in the PES group vs 6.1% in the corresponding BMS group. The authors concluded that both longer-and larger studies were needed to understand how these infrequent, but potentially deadly events could be prevented.

In a further pooled analysis of four randomized trials (RAVEL, SIRIUS, C- and E-SIRIUS) Spaulding et al (62) that compared SES and BMS in 1748 patients with 4 years follow-up again there were no significant differences in the rates of death, MI, or ST in the two groups. According to the ARC definition, 30 ST were found in the SES and 28 in the BMS group. ST was more frequent in the BMS group in the first year (11, vs. 3 in the SES group, p=0.03), whereas very late ST was more frequent in the SES group (23, vs. 14 in the BMS group, p=0.14). Significant heterogeneity was found in patients with diabetes. The 4-year cumulative survival rates was significantly in the SES group (87.8%, vs. 95.6% in the BMS groups, p=0.008). Although no clear pattern of mortality was identified, among the patients with diabetes, there was a small excess of very late ST in the SES group (11 patients, vs. 3 in the BMS group).

In conclusion, the clinical outcomes of large scale meta-analyses did not reveal any significant differences in death rates between BMS and DES during long-term follow-up to 5 years. It was hypothesized that the small increase in very late ST seen with DES was balanced by a somewhat smaller early ST rate than BMS, together with less frequent need for repeated revascularization...
procedures, and fewer associated complications, compared with BMS. However, groups of DES and BMS differed widely with respect to cardiovascular risk factors such as diabetes, number of stents, stent diameter, stent length, and target lesion location, limiting the value of adjustments made by propensity score analysis. Therefore this does dissipate concern that the use of DES in more complex “real life” patients and lesion subsets, not represented in the randomized clinical trials, may be associated with higher adverse event rates especially late after the PCI.

Registry data support the notion however that overall there is no significant difference between DES and BMS in ST

- Long-term follow-up data of 8146 patients treated with DES in 2 academic institution (63) showed that angiographically documented ST, observed in 152 patients, occurred at a median of 9 days and accrued at a steady rate of 0.6% per year between 30 days and 3 years of follow-up. Late ST was encountered steadily with no decrease up to 3 years follow-up. Early and late ST was observed with SES and with PES. Acute coronary syndrome at presentation and diabetes were independent predictors of ST. During extension of the follow-up period, Wenaweser P (64) identified that late ST occurred steadily at an annual rate of 0.4% to 0.6% for up to 4 years with an incidence density of 1.0/100 patient-year and a cumulative incidence of 3.3%. Rates of death, MI, and the composite of death or MI were 10.6%, 4.6%, and 14.6%, respectively, in the overall population. During the entire observation period of 4 years, 27 patients suffering from definite ST subsequently died. There was no BMS arm in this observational study.

- In the Western Denmark Heart Registry, 12,395 consecutive patients treated with stent implantation were followed for 15 months. DESs were implanted in 3,548 patients (5,422 lesions) and BMS were implanted in 8,847 patients (11,730 lesions). Definite, probable, or possible ST was found in 190 (2.15%) patients in the BMS group and in 64 (1.8%) patients in the DES. Very late definite ST occurred more frequently in patients receiving DES. The risk of MI between 12 and 15 months after implantation was higher in the DES group but mortality was similar in the two groups. The authors conclude that “the minor risk of ST and MI within 15 months after implantation of DES seems unlikely to outweigh the benefits of these stents” (65).

- The DEScover Registry collected data from 6906 patients who underwent PCI in the United States with follow up to 1 year. Patients (94%) were treated with DES (SES or PES). Substantial baseline differences were observed between patients receiving BMS compared with those treated with DES. In the BMS group the patients were older and more often had a previous history of CABG. Acute MI was more frequent the indication for stenting compared to the DES group. Finally, left ventricular function was lower among BMS patients. Rates for ST were low (<1%) for both groups and did not differ significantly. Adjusted 1-year HRs comparing BMS with DES did not differ significantly for either death or MI (66).

- In the Swedish Coronary Angiography and Angioplasty Registry (SCAAR), 6033 patients were treated with DES and 13,738 patients with BMS with outcome analysis data up to 3 years (67). In contrast, to the studies above, DES implantation was associated with an increased risk of death, as compared with BMS. This trend was evident after 6 months, when the risk of death was 0.5% higher and a composite of death or MI was 0.5 to 1.0% higher per year.
However for reasons that have not yet been explained this trend was reversed at one year data review with a trend to benefit towards DES.

The registry data overall thus tends to support the notion that there is either no clinical difference in ST between DES and BMS. Other Registries such as GHOST and New York (68,69) suggest that there may even be a benefit favoring DES.

**DES v DES**
- The REALITY trial (70) which randomised patients to Sirolimus or Paclitaxel eluting stents suggested a non-significant increase in stent thrombosis in the PES group (0.6% versus 1.6% p=0.07)

Irrespective of incidence and any difference or not between DES and BMS ST is an important clinical event and needs serious consideration.

### 2.3 Timing of ST and duration of anti-platelet therapy

Iakovou and colleagues (55 Iakovou and) have analysed predictors for ST in a prospective observational cohort, where 2229 consecutive patients underwent successful implantation of DES or PES. Patients were given an antiplatelet regime with aspirin continued indefinitely and ticlopidine or clopidogrel for at least 3 months after SES and for at least 6 months after PES implantation. The study was designed using ST as the main outcome (early ST from procedures end up to 30 days, late ST over 30 days, and cumulative ST). After 9-months follow-up, 29 patients had ST (9 with SES and 20 with PES, p=0.09). Of these, 14 patients had early and 15 late ST. The study revealed that independent predictors of ST were: premature discontinuation of antiplatelet therapy (hazard ratio 89.78), renal failure (HR, 6.49), bifurcation lesion (HR, 6.42), diabetes (HR, 3.71), and a lower ejection fraction (HR, 1.09) at entry. It is perhaps not surprising that complex lesions and patients are now treated with DES. Their widespread availability has broadened the scope of PCI. In the Iakovou study, 27% of the population had diabetes and 79% of the lesions were complex. Consequently, the clinical implications of ST were severe, with a case-fatality rate of 45% (amongst all the 29 patients with ST, 13 died). Overall the most important predictor of ST after implantation was premature discontinuation of the antiplatelet therapy. Thrombosis occurred in 29% of patients who prematurely discontinued dual antiplatelet therapy, making adherence to treatment of paramount importance. The incidence of ST at 9 months after DES implantation in consecutive real-world patients was 1.3%.

The other major study investigating predictors for ST is the one from Airoldi and colleagues (71). Before this study the incidence and predictors of ST were evaluated during relatively short follow-up periods, limited to 6 to 12 months and few data were available on the incidence of ST 1 year after DES implantation. Dual antiplatelet therapy to prevent ST was also been recommended in the first 3 to 6 months after DES implantation, and no data were available on its utility over a longer time period. Airoldi and colleagues selected as outcome delayed ST in a 18 months follow-up study. This was a prospective observational study on 3021 patients consecutively and successfully treated with DES. The incidence of ST throughout follow-up period and its relationship with thienopyridine
therapy was analyzed. ST occurred in 58 patients (1.9%) at 18 months. 42 patients (1.4%) experienced the event within 6 months after stent implantation. Acute MI (fatal and non fatal) occurred in 46 patients and death in 23 patients with ST. The median interval from discontinuation of thienopyridine therapy to ST was 13.5 days for the first 6 months and 90 days between 6 and 18 months. On multivariate analysis, the strongest predictor for ST within 6 months of stenting was discontinuation of thienopyridine therapy (HR, 13.74) but after 6 months this did not predict the occurrence of ST. A very important finding stressing the relevance of other factors such as procedural variables was that 50% of the thrombotic events occurred in the first 30 days after DES implantation. This implies that improved implantation technique and screening for antiplatelet resistance may have a role in reducing early ST.

Late or very late ST seems to be almost unique to DES.

However
- Just how long dual anti-platelet therapy should be continued for is unresolved. Further, what to do about those needing to stop such drugs for non-cardiac procedures and operations, versus the risk of stopping, is unclear.
- Long term DAPT therapy in some patients is associated with increased bleeding. In CAPRIE the incidence of GI bleeding was 0.72 % with aspirin and 0.52 % with clopidogrel. More recently, GI bleeding with combination therapy has been shown to be increased 7-fold compared to controls [72] although most can be managed conservatively

2.3.1 Dual antiplatelet therapy as a major factor influencing the rate of ST

One major factor highlighted in the Iakovu and Airoldi studies was the lack of understanding regarding the optimal duration of dual anti-platelet therapy. Dual anti-platelet therapy is currently recommended for 1 month after BMS, and 12 months after DES. However, there is uncertainty regarding the risk of clinical events after discontinuation of clopidogrel, particularly in the case of DES implantation.

BASKET-LATE (73) analysed consecutive series of 746 nonselected patients surviving 6 months without major events and followed them for 1 year after discontinuation of clopidogrel. Rates of 18-month cardiac death/MI were not different between DES and BMS patients. However, after discontinuation of clopidogrel, these events occurred in 4.9% after DES versus 1.3% after BMS implantation. Documented late ST and related death/target vessel MI were twice as frequent after DES versus BMS (2.6% vs. 1.3%). Thrombosis-related events occurred between 15 and 362 days after discontinuation of clopidogrel, presenting as MI or death in 88%. This prospective randomized comparison of DES versus BMS in a ‘real-world’ setting shows that the incidence of late cardiac death or nonfatal MI after discontinuation of clopidogrel is greater in DES- as compared with BMS-treated patients. Most of this difference was attributed to an increased rate of thrombosis-related events, which carried a much higher risk of cardiac death or nonfatal MI. At inclusion, the BASKET-LATE patients had more complex lesions (almost 60% had acute coronary syndrome) and clopidogrel was discontinued in all patients after 6 month with no protocol driven angiograms allowed. Several of these high-risk characteristics turned out to be good predictors of late thrombosis-related events (these included stenting of bifurcation or bypass-graft lesions).
The findings of BASKET-LATE may have major clinical implications. Discontinuation of the antiplatelet therapy could account for the higher rate, compared with BMS use, of late death or nonfatal MI, presumably related to thrombosis. According to these authors nonselected patients, implantation of DES would avoid 5 major cardiac events at 6 months in 100 patients treated but lead to 3 patients suffering cardiac death or nonfatal MI during months 7 to 18. Obviously, it can be argued whether prolonged dual antiplatelet therapy may be beneficial in all or even at all. However, the wide time window in which these thrombotic events occur may question a direct relation of clopidogrel discontinuation. Both the risk of bleeding because of prolonged dual antiplatelet therapy (up to 2% per year) and the increased financial cost would have to be taken into account if we were to prescribe DAPT for prolonged periods. Therefore, a prolonged dual antiplatelet therapy may only be worthwhile in patients at high risk for late ST especially in the light of other studies that suggest most of the impact of DAPT is within the first 30 days – 6 months.

New antiplatelets regimes, other stent types (e.g., bioabsorbable or endothelialisation promoting agents) or other drugs/drug dosage or drug release kinetics of DES and an understanding of the importance of excellent procedural technique may change the risk of early and late ST. It may also be important to indentify individual patient factors such as aspirin or clopidogrel resistance, or drug-drug interactions and to treat affected patients in a specific tailored way.

2.3.2 Duration of dual antiplatelet treatment

The optimum duration of dual antiplatelet treatment must balance the benefit of reduced ischemic events against the harm from increased bleeding episodes as well as the cost of long term therapy.

While some studies now suggest that treatment should be prolonged for at least 2 years others suggest that the most important time for obsessional continuous DAPT is early (ie in the first 6 months). Treatment with aspirin and clopidogrel for 12 months provided a 27% reduction in the relative risk of death, myocardial infarction, or stroke in patients undergoing PCI, compared with a 1-month regimen (p=0.02) in the CREDO trial. In the Duke study (74) which analysed 2-year mortality in patients treated with DES, the outcome was lowest for those who remained on clopidogrel for at least 1 year and was highest in individuals not on this drug at 1 year. Findings of other registry studies have indicated the excess mortality follows termination of clopidogrel within 6-12 months after implantation of DES.

Notably, most of the bleeding risk with dual antiplatelet regimens seems to come fairly early after initiation of treatment. Data from CHARISMA trial (75) showed similar rates of moderate-to-severe bleeding after dual antiplatelet treatment compared with aspirin alone beyond 270 days. Thus, a patient who has tolerated a dual regimen for 9-12 months, without occurrence of any bleeding episodes that led to a doctor stopping treatment or the patient discontinuing the regimen themselves, has essentially passed a so-called bleeding “stress test”. The CHARISMA analysis suggests that such individuals are unlikely to have an appreciable incremental bleeding risk with an extended duration of dual antiplatelet treatment compared with the baseline risk with aspirin alone. Therefore, available data lend to support to uninterrupted dual antiplatelet treatment for at least 1 year. Whether a longer regimen would provide additional benefit with acceptable bleeding risk is unknown. Only a prospective randomised clinical trial (as has been proposed by the FDA) can properly address this question. The bleeding risk may, of course, be attenuated by the increased use of the radial approach at PCI to avoid femoral artery complications.
2.4 ST SUMMARY

- **In summary** it is unclear whether there is *clinically* significant problem of ST with DES compared with BMS especially late after the procedure where patients treated with DES seem to suffer more (albeit small number) of ST; the likely scenario appears to be that there are more ST with BMS patients early but that there may be an excess and as yet un-plateaued higher incidence of late ST with DES -data suggests that overall there are no excess adverse clinical events due to ST in those treated with DES (maybe because restenosis with BMS leads to occlusive acute disease (76)).

- Equal number of events occur early (within the first 30 days) either with DES or BMS

- At least 50% of all ST (BMS DES) occur early

- We do not know how long in the long term to recommend dual anti-platelet therapy for, and in which patients and what to recommend when patients need a non-cardiac surgical procedure. This will require further trial data.

- Clopidogrel has limitations as an anti-platelet agent – in particular there is concern regarding the potency especially in the early period post procedure when most events occur and when the stimulus to stent thrombosis is greatest. At this time issues such as poor stent apposition leading to a high risk of occlusive thrombus could be overcome somewhat by excellent technique (high balloon pressures, post dilatation, use of intra-vascular ultra-sound to ensure good stent wall apposition) but maybe also the use of more potent anti-platelet agents may attenuate those non-modifiable factors.

More recently, in a three-year follow-up of BASKET (Pfisterer M, European Heart Journal 2009), all 826 consecutive BASKET patients were further observed after 3 years to assess the long-term benefit-risk ratio of DES vs. BMS relative to stent size. Data were analysed separately for patients with small stents (<3mm vessel/<4mm bypass graft) vs only large stents (>3mm native vessel). Clinical events were related to ST. Cardiac death/MI rates were similar, however, death/MI beyond 6 months was higher with DES (9.1% vs 3.8% BMS, p=0.009), mainly due to increased late death/MI in patients with large stents. The results paralleled findings for ST. Based on randomized data, the findings of this long-term study suggest that **baseline stent size** seems to determine the long-term benefit-risk balance in a relevant way: patients with at least one small stent have a large benefit of DES in all clinical endpoints, which is not significantly reduced by late ST-related events up to 3 years. In contrast, patients with large stents have a small clinical benefit on restenosis-related events only and, therefore, late ST-related problems become relevant after 3 years. It remains uncertain how this will translate into even longer-term outcome balance which, however, will also be affected by the natural progression of underlying coronary disease. This uncertainty and the possible impact of newer DES on this benefit-risk balance, particularly regarding the large group of patients in need of large stents in daily practice, is addressed prospectively in the ongoing European multicentre BASKET-PROVE, in which 2323 consecutive patients with large vessel stenting were randomized to a first vs. a second generation DES vs. a BMS (results expected in 2010).

These findings support the previous NICE guidance on DES that the best outcome is when they are used in those particularly at risk of re-stenosis. It would suggest also that those for prolonged potent DAPT should also be the same group.

- Irrespective of length of time that DAPT is required for it is clear that absence of thienopyridine is a risk factor for ST especially within the first 6 months and one group of
patients who in effect have sub-optimal dosing of clopidogrel are those with so called clopidogrel resistance.

3.0 CLOPIDOGREL: Limitations for standard dosing in clinical practice
(This is reviewed in detail in Hobson and Curzen Thrombosis and Haemostasis 2009;101:23-30)

3.1 Clopidogrel resistance

3.1.1 Clopidogrel Resistance: Laboratory Observations

There is wide inter-individual variation in clopidogrel response. Currently, no laboratory definition of true clopidogrel resistance is universally accepted. It is agreed that clopidogrel resistance occurs when the drug is unable to achieve its target pharmacologic effect which is inhibition of platelet activity (IPA). Since there are a number of different assays that can be used to assess this parameter it follows that there are a number of empiric cut-off values that have been adopted to suggest non-responsiveness. None of these tests have been fully standardised to measure clopidogrel responsiveness leading to significant inter-laboratory variation in results. Prevalence figures for non-responders to clopidogrel therefore range from 4-30 per cent at 24-hours after drug administration; variation being to some degree dependent on the technique used to measure platelet aggregation and the presence of factors contributing to greater baseline platelet reactivity (77-82). Furthermore, such lab-based assays have the disadvantage that they tend to look at platelet function in isolation whereas the question asked by the physician relates to the tendency for the patient in front of them to clot their whole blood, which incorporates a much more complex mechanism than platelets on their own. What is certain is that the reported prevalence of clopidogrel resistance from laboratory measurements of isolated platelet activity is much higher than that seen in whole blood near patient assays, and it is the latter that better predict adverse events.

Light transmittance aggregometry (LTA) is considered the historical gold standard for assessing platelet function. It uses spectrophotometric measurement of platelet aggregation in platelet-rich plasma in response to ADP as an agonist. The procedure carries with it a number of drawbacks since it is labour-intensive, requires expert personnel, has time-consuming centrifugation steps which may injure platelets, tests in an artificial milieu devoid of red and white blood cells, and can be subject to several inter-laboratory differences (eg dose of agonist, type of anticoagulant and timing of measurements (78).

Impedance aggregometry, on the other hand, uses electrical resistance between two electrodes immersed in whole blood to measure platelet aggregation. It offers improved sensitivity over LTA as a result of no centrifugation step and hence no platelet injury; inclusion of giant platelets for functional assessment, and a shorter time to perform the test under more physiological conditions (83,84).

3.1.2 Clopidogrel Resistance: Clinical and Epidemiological Observations

Several studies have investigated variability in platelet response to clopidogrel. It has been thus been established that relative clopidogrel resistance not only occurs but is also linked to adverse
clinical events. Common to all studies, however, are the relatively small sample sizes and short follow-up periods and have not been sufficiently powered to detect a causal association.

One of the largest studies found a normal distribution of clopidogrel responsiveness amongst 544 individuals consisting of healthy volunteers, patients after coronary stenting, those with heart failure, and after stroke and subsequently categorised hypo-responders, hyper-responders and the remaining individuals as standard responders using the mean IPA achieved as a reference point (78). Another prospectively studied 60 patients who underwent primary PCI following an ST-elevation myocardial infarction to determine whether variability in response to clopidogrel affected clinical outcomes. Patients were stratified into four quartiles according to the percentage reduction of ADP induced platelet aggregation. 40 per cent of patients in the first quartile, who were considered non-responders, sustained a MACE during six months follow-up compared to one patient in the second quartile and none in the third and fourth (85). The largest study (86) so far looked at platelet reactivity following clopidogrel administration in 804 patients who had received DES during PCI. The authors found that patients with >70 per cent post-clopidogrel in vitro platelet aggregation had a nearly four-fold increase in definite or probable stent thrombosis as compared with clopidogrel responders.

A number of recent studies have demonstrated an association between low response to clopidogrel and ST following DES (87). ST is likely to be multifactorial and resistance to clopidogrel therapy may well be one of the factors in some patients. The important thing about this is that there is currently absolutely no attempt to identify patients who are not responding to standard clopidogrel doses. Theoretically it would be possible therefore to minimise the risk associated with clopidogrel resistance by measuring the response to the drug in all patients undergoing stent implantation and then tailoring therapy to that response—whether it be by higher doses of clopidogrel or the use of a more potent anti-platelet agent.

3.1.3 Clopidogrel Resistance: Possible Mechanisms

Several mechanisms for clopidogrel resistance have been postulated and encompass genetic, cellular and clinical factors either acting singly or in conjunction. Clinical factors can range from poor drug compliance to suboptimal stent deployment and increased baseline platelet reactivity due to increased body mass index, diabetes mellitus and insulin resistance (79,88,89).

Again such studies suffer small sample sizes, empirical cut-off points for responsiveness, lack of robust clinical outcome data, differing methods of assessing platelet aggregation and not surprisingly contradictory findings exist. No one mechanism has as yet been accepted as the true cause of clopidogrel resistance. Of particular interest has, however, been that several functional polymorphisms are found in genes encoding cytochrome P450 isoenzymes involved in the hepatic biotransformation of clopidogrel to its active form. Abnormal function variants of the CYP2C9 and CYP2C19 genotypes have been associated with a decreased pharmacodynamic response to clopidogrel resulting in less exposure to the active metabolite (90,91).

The relationship between these genotypes and their corresponding pharmacodynamic effect must now be confirmed in larger cohorts and a link to clinical outcomes established.
4.0 PRASUGREL

4.1 Prasugrel: What is it and why is it of potential clinical benefit in PCI?

Prasugrel, like clopidogrel, is a thienopyridine that selectively and irreversibly inhibits the P$_{2}Y_{12}$ ADP platelet receptor. Like clopidogrel, it is also a prodrug but requires a single cytochrome P450-dependent oxidative step to generate its active metabolite compared to the two required by clopidogrel (892). Importantly, prasugrel has been shown to have a faster, more potent and consistent effect upon IPA than clopidogrel (93-99). Data from the laboratory and in patients show a more rapid onset of inhibition of platelet activity than is seen with clopidogrel that is due to faster bioavailability of the active metabolite. The onset of this effect in patients is within an hour of an oral loading dose. Importantly, there is a much less heterogeneous response to prasugrel in patients, even in those who have exhibited clopidogrel resistance previously (100). These properties make prasugrel potentially useful for at least some patients undergoing PCI. Just on the basis of these data one would postulate that, bearing in mind the requirement for preloading of clopidogrel to ensure its optimal effect and the (unmeasured!) heterogeneity exhibited in response to it, patients undergoing emergency stent implantation and those whose response to clopidogrel is poor would benefit from this newer drug.

Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 (PRINCIPLE-TIMI 44) was a randomized, double-blind, 2-phase crossover study of prasugrel compared with high-dose clopidogrel in patients undergoing cardiac catheterization for planned percutaneous coronary intervention. The primary end point of the loading-dose phase (prasugrel 60 mg versus clopidogrel 600 mg) was IPA with 20 mumol/L ADP at 6 hours. Patients with percutaneous coronary intervention entered the maintenance-dose phase, a 28-day crossover comparison of prasugrel 10 mg/d versus clopidogrel 150 mg/d with a primary end point of IPA after 14 days of either drug. In this study, 201 subjects were randomized. IPA at 6 hours was significantly higher in subjects receiving prasugrel (mean+/−SD, 74.8+/−13.0%) compared with clopidogrel (31.8+/−21.1%; P<0.0001). During the maintenance-dose phase, IPA with 20 mumol/L ADP was higher in subjects receiving prasugrel (61.3+/−17.8%) compared with clopidogrel (46.1+/−21.3%; P<0.0001). Results were consistent across all key secondary end points; significant differences emerged by 30 minutes and persisted across all time points.

Among patients undergoing cardiac catheterization with planned percutaneous coronary intervention, loading with 60 mg prasugrel resulted in greater platelet inhibition than a 600-mg clopidogrel loading dose. Maintenance therapy with prasugrel 10 mg/d resulted in a greater antiplatelet effect than 150 mg/d clopidogrel.(101)
4.2 TRITON-TIMI 38

4.2.1 Design

TRITON-TIMI-38, a large multi-centre clinical outcomes trial involving ACS patients comparing clopidogrel to prasugrel, has recently reported (102).

The study recruited 13608 patients with acute coronary syndromes who were committed to PCI as part of their treatment and randomised them to receive either prasugrel (loading dose 60mg followed by 10mg maintenance) or clopidogrel (300mg loading dose followed by 75mg) for 6 to 15 months. 10074 of the patients had non-ST elevation ACS and 3534 had ST-elevation MI. The primary efficacy endpoint consisted of the combination of: death from cardiovascular causes, non-fatal MI and non-fatal stroke. The key safety endpoint was major bleeding.

The trial design is important in order to understand subsequent analysis. Patients could only be randomised into the trial when their coronary anatomy had been documented by angiography because they had to be committed to PCI. The loading dose of study drug was then administered “anytime between randomisation and 1 hour after leaving the cardiac catheter laboratory”. In practice, this meant that “nearly all patients (99%) had PCI at the time of randomisation...” Specifically, “The study drug was administered before the first coronary guidewire was placed in 25% of patients, after the first coronary guidewire was placed and during PCI or within 1 hour after PCI in 74%, and more than 1 hour after PCI in 1%”. Given the established data, presented earlier, that clopidogrel loading is more efficacious at a 600mg dose and that there is clear cut benefit from giving clopidogrel as early as possible before a PCI procedure, then this design requires some scrutiny.

4.2.2 Results

- The headline result for the study was that the primary endpoint occurred significantly less frequently in the prasugrel group (12.1% clopidogrel versus 9.9% prasugrel; p<0.001). Assessment of the original New England Journal publication (N Engl J Med 2007;357:2001-15) reveals that the dominant component of the difference between the groups for this primary endpoint was non fatal MI ... in fact this was the only one of the 3 parts of the combined primary endpoint that was significantly different. This non-fatal MI was largely composed of peri-procedural enzyme rise, as can be seen by the timing of the separation of the event curves which is within the first part of the first day after randomisation. The major part of the difference between the curves is generated at this time.

- There were also significantly fewer ST events in the prasugrel group during follow up with 68 (1.1%) compared to 142 (2.4%) in the clopidogrel group (p<0.001). It is not possible to determine the exact timing of the ST events from this paper, but most occurred within the first 30 days.

- The rate of life-threatening bleeding was also significantly higher in the prasugrel group (1.4% versus 0.9%; p=0.01) as was fatal bleeding (0.4% versus 0.1%; p=0.002).

- Post hoc, non-pre-specified analyses yielded possible subgroups who would be at particularly high risk of bleeding with prasugrel, including the elderly, those with very low body weight and those with previous TIA/stroke.
A further issue in relation to safety is that, overall 33 people died from malignant cancer in the Prasugrel arm compared with 21 in the clopidogrel arm, while malignant tumours were detected in 61 Prasugrel patients compared with 41 in the clopidogrel group. Existing malignancies were as common in one group as in the other in TRITON, but there were 27% more tumours of new onset during the trial in the Prasugrel group including highly metastatic lung and breast cancers.

It should be noted that there was no difference in overall mortality between the two groups.

**Summary**

In patients with ACS scheduled for PCI, Prasugrel therapy was associated with significantly reduced rates of MACE including ST (but as a sub-study) and essentially early but with an increased risk of major bleeding including fatal bleeding. Efficacy was particularly evident in the diabetic sub-group.

Overall mortality between the clopidogrel and prasugrel treatment arms did not differ significantly.

### 4.2.4 What are the weaknesses of current aspirin and clopidogrel therapy for coronary intervention that may be addressed by prasugrel?

- **Variance in patient response to clopidogrel**: individual patient-to-patient variability renders those with the lowest response at risk of thrombotic complications including peri-procedural MI and ST. As we do not assess which those patients are, treatment with prasugrel may provide more homogeneous anti-platelet effect.

- **Most ST occurs early**. It is due to a combination of a number of factors including inadequate technique (stent wall apposition) which may be operator dependant but also may be due to the lesion stent conformability issues. Within the first 30 days most occur within the first 24 hours - the time of the most highly thrombotic milieu, and in particular in those most thrombogenic (STEMI, NSTEMIs) all against a background of potent clopidogrel resistance.

- **Some patients require their PCI with such urgency that it is unlikely that they will have attained adequate clopidogrel activity before the stent is placed** (eg primary PCI for ST elevation MI). This increases the risk of peri-procedural enzyme rise and ST. A faster acting agent may be of benefit for such clinical scenarios.

**How will a new P2 Y12 receptor inhibitor help**

- It may over come the significant excess early hazard as shown in TRITON, and have an impact on the lower incidence of events that then occur out to one year (and beyond). TRITON demonstrated superiority of outcome, albeit with potential excess bleeding in some patients, over clopidogrel and was the next logical trial after CURE, PCI-CURE CREDO, and CLARITY.

- **There appears to be a need for a more potent AP agent**

**What are the issues with Prasugrel**

- **Excess bleeding risk**
  - This may be somewhat attenuated but not completely overcome by the increase use of the radial access site approach. Some of the bleeding side effects are related to femoral access site – however late spontaneous bleeding probably accounts for >30% of excess bleeding.
Limited use in those with previous TIA, low body weight or the elderly

- **What are the benefits of Prasugrel**
  - Prasugrel appears a good drug in terms of pharmacology and pharmacokinetics with a very good metabolization profile and probably less bone-marrow toxicity
  - Potency for dealing with a real clinical problem that results in death and AMI
  - In the HORIZONS study (103) (Use of Bivalirudin in patients undergoing PCI for STEMI) benefit of was shown with bivalirudin over Abciximab (ReoPro - Glycoprotein IIbIIIa receptor inhibitor). Much of the benefit was in the bleeding outcomes, which were less with Bivalirudin than Abciximab and which directly correlated to late outcomes. Therefore it is likely there will be an uptake of bivalirudin. However the downsides are that there was an early hazard with excess ST which may in part be due to the balance between thrombotic milieu, inadequacy of clopidogrel and especially in the context of less time to pre-load (these are acute STEMI patients). In such circumstances use of a more potent APT such as Prasugrel may overcome the early ST

What are the weaknesses of the TRITON study design that could have influenced the results?

- The comparison was made using what is considered in modern practice to be an inadequate accepted loading dose of clopidogrel (in fact none) : the fist dose was given either during or after the PCI in all the patients, despite the fact that in the majority the procedure was not an emergency and the clopidogrel loading would have been given at least 24 hours before that in routine practice. Since it is well-established that clopidogrel loading can reduce periprocedural MI and early ST when given at 600mg at least 6 hours and preferable 24 hours before the procedure then TRITON has been designed in a manner that has failed to exploit this proven standard of care of clopidogrel.

- The clinical benefit associated with prasugrel was less than implied by conventional analyses. The primary endpoint benefit was clearly driven by nonfatal MI. This parameter is not necessarily associated with a mortality outcome and is arguably the least important of the composite end point, especially because a less stringent definition of MI was used than is the case in many studies. In fact, without introducing and adding the artificial surrogate end point of 'enzymatic MI' to the real MIs that were properly identified and reported by TRITON investigators, the trial is negative, not positive. Clearly the long-term bleeding and cancer risks may not be justified by the vascular-outcome benefit. It is also likely that a 600mg clopidogrel loading dose more than 6 hours before the PCI may have have had an important bearing upon the frequency of non fatal MI in this group.
What are the safety implications of prasugrel from TRITON?

♦ The rates of both fatal and life-threatening bleeding were significantly higher in the prasugrel group. This has to be a cause for concern, particularly in the light of the considerations about what was driving the apparent benefit of prasugrel in this study. The ad hoc analyses of high risk sub groups are useful but demand specific investigation.

♦ The recommendation of the drug manufacturer, partially supported by the recent FDA panel, that such patients should be given a 5mg maintenance dose instead of 10mg in order to limit bleeding risk, is based upon no available evidence and may be less than acceptable. Further trial data addressing dosing may well be required to provide robust and persuasive reassurance in relation to widespread use of prasugrel if its main benefit relates to peri-procedural enzyme rise.

♦ This needs to be balanced against the need to reduce early pro-thrombotic stimuli.

♦ There are concerns raised through the trial regarding cancer risk in prasugrel patients.

♦ Clinicians are surprised that the FDA panel approved the drug unanimously without referral to its safety committee machinery. Caution is advised in relation to safety pending more data.

♦ Definition of AMI – these were both clinically relevant as well as enzyme driven MIs. This would suggest the risk benefit is weighted since the risk is bleeding. Further the MIs were trial committee adjudicated which is reasonable in such a study but make skew benefit

Who are we likely to use Prasugrel in?

Given the potency and speed of onset of this drug as well as its consistency of effect, there are already some subgroups that may benefit from its applications:

- Patients with previous stent thrombosis
- Patients who can be detected as having clopidogrel resistance
- STEMI (perhaps especially those treated with Bivalirudin in patients undergoing primary PCI, especially if this is performed via the radial artery to eliminate femoral artery bleeding complications) since there is an excess of ST in these patients compared to iv GP IIbIIIa inhibitor Abciximab.
- Diabetics
- If there were a desire to truly impact on early events that exist despite clopidogrel therapy

How long would we use it for?

The data suggests that if we are to use Prasugrel instead of clopidogrel it should be according to the trial criteria. However, further trial data are required to answer this question with any accuracy. Early and limited therapy to overcome the early thrombotic hazard but not encounter the longer term bleeding risk may be worth considering but is unproven
### EVENT RATES IN TRITON

#### Major efficacy and safety end points at 30 days

<table>
<thead>
<tr>
<th>End point</th>
<th>Clopidogrel (%)</th>
<th>Prasugrel (%)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular death, nonfatal MI, and nonfatal stroke</td>
<td>9.5</td>
<td>6.8</td>
<td>0.68 (0.54-0.87)</td>
</tr>
<tr>
<td>Cardiovascular death, nonfatal MI, and TVR</td>
<td>8.8</td>
<td>6.7</td>
<td>0.75 (0.59-0.95)</td>
</tr>
<tr>
<td>Cardiovascular death and MI</td>
<td>8.8</td>
<td>6.2</td>
<td>0.70 (0.55-0.90)</td>
</tr>
<tr>
<td>MI</td>
<td>7.0</td>
<td>4.9</td>
<td>0.70 (0.53-0.92)</td>
</tr>
<tr>
<td>TLR</td>
<td>1.9</td>
<td>1.3</td>
<td>0.66 (0.39-1.14)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.9</td>
<td>0.4</td>
<td>0.43 (0.18-1.06)</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>2.4</td>
<td>1.2</td>
<td>0.48 (0.28-0.84)</td>
</tr>
<tr>
<td>TIMI major bleeding unrelated to CABG surgery</td>
<td>1.3</td>
<td>1.0</td>
<td>0.74 (0.39-1.38)</td>
</tr>
</tbody>
</table>

#### Major efficacy and safety end points at 15 months

<table>
<thead>
<tr>
<th>End point</th>
<th>Clopidogrel (%)</th>
<th>Prasugrel (%)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular death, nonfatal MI, and nonfatal stroke</td>
<td>12.4</td>
<td>10.0</td>
<td>0.79 (0.65-0.97)</td>
</tr>
<tr>
<td>Cardiovascular death, nonfatal MI, and TVR</td>
<td>12.0</td>
<td>9.6</td>
<td>0.79 (0.65-0.97)</td>
</tr>
<tr>
<td>Cardiovascular death and MI</td>
<td>11.5</td>
<td>8.8</td>
<td>0.75 (0.61-0.93)</td>
</tr>
<tr>
<td>MI</td>
<td>9.0</td>
<td>6.8</td>
<td>0.75 (0.59-0.95)</td>
</tr>
<tr>
<td>TLR</td>
<td>3.2</td>
<td>2.2</td>
<td>0.70 (0.45-1.06)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.5</td>
<td>1.6</td>
<td>1.03 (0.60-1.79)</td>
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<tr>
<td>Stent thrombosis</td>
<td>2.8</td>
<td>1.6</td>
<td>0.58 (0.36-0.93)</td>
</tr>
<tr>
<td>TIMI major bleeding unrelated to CABG surgery</td>
<td>2.1</td>
<td>2.4</td>
<td>1.11 (0.70-1.77)</td>
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</tbody>
</table>
References


44. NICE guidelines for the use of drug-eluting stents: how do we establish worth? de Belder MA; National Institute of Health and Clinical. Heart. 2008 Dec;94


