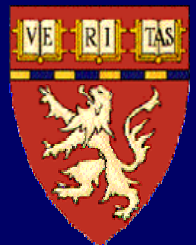


# Dual Antiplatelet Therapy (DAPT) Randomized Trial

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# Clinical Significance of the DAPT Study

- Uncertainty regarding optimal duration of thienopyridine therapy after DES has lead to wide variation in clinical practice
  - 12m recommended by AHA/ACC society guidelines
  - Some physicians continuing indefinitely for possible prevention of very late stent thrombosis
- Observational studies suggest possible benefit to >12m, but no randomized studies have defined the optimal duration of DAPT for DES safety
- Such a study will require a substantial effort
- Whether positive or negative, it will have significant impact

# **DAPT and DES**

## ***Clinical Areas of Equipoise***

- **Is it better to continue >1y?**
  - **Balance of safety and efficacy**
- **If so, is this benefit specific to DES or more general?**

# DAPT Study Objectives

## Primary

- To compare a total of 12 m vs. 30 m of DAPT in DES subjects who are event free at 12 months

## Secondary

- To discriminate if effect of prolonged DAPT is the same for subjects treated with DES vs. BMS

# DAPT RCT Study Flow Chart

Initial  
Procedure –  
Enrollment

Randomization  
(All Eligible Subjects)

End of  
Treatment

End of  
Follow Up

0 m

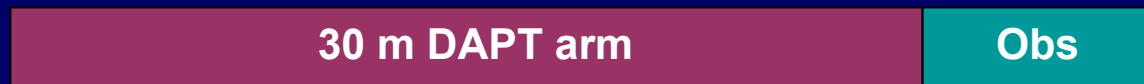
6 m

12 m

15 m

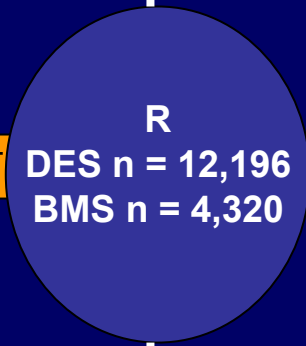
30 m

33 m



## Double Blind Placebo Controlled RCT

- 12 vs 30m DAPT in subjects clear at 12m
- Co primary endpoints: ST and MACCE, Secondary endpoint: Major bleed
- 33 months follow up, to include 3 month “rebound period”
- Simultaneous RCT of 12 vs 30m DAPT in BMS
- Operator defined stent and thienopyridine choice (either clopidogrel or prasugrel)



Open label DAPT



Patients with MACCE or major bleed followed to 12m, but ineligible for 12m randomization



# DAPT Study Endpoints

## **Primary clinical endpoint:**

Composite of all death, myocardial infarction (MI) and stroke (defined as MACCE)

## **Primary stent thrombosis endpoint:**

ARC definite or probable stent thrombosis (ST)

## **Safety (secondary) endpoint:**

Major bleeding (GUSTO classification, severe and moderate bleeding combined)

# Rationale for Co-Primary Endpoints

- **Two potential mechanisms of benefit of 30m of DAPT:**
  - Device oriented (reduction in ST)
  - Patient oriented (disease progression/non-target lesion events)
- **Treatment differences may not be detectable by both endpoints**
  - treatment difference for clinical endpoint may not be mediated by ST prevention, or
  - a true treatment difference in ST may not be detected as a difference in the clinical endpoint
- **Co-primary endpoints allow preservation of overall alpha level of 0.05, while allowing a significant results for either or both endpoints to yield a successful study**

# DAPT RCT Sample Size

## MACCE Hypothesis

$$H_o: \lambda_{12m \text{ DAPT}} = \lambda_{30m \text{ DAPT}}$$

$$H_A: \lambda_{12m \text{ DAPT}} \neq \lambda_{30m \text{ DAPT}}$$

**Assumptions:** Annual rate of MACCE during 12 - 30 m = 2.9% for 12m DAPT and 2.175% for 30m DAPT; during 30 –33 m hazard ratio = 1.

## Stent Thrombosis Hypothesis

$$H_o: \lambda_{12m \text{ DAPT}} = \lambda_{30m \text{ DAPT}}$$

$$H_A: \lambda_{12m \text{ DAPT}} \neq \lambda_{30m \text{ DAPT}}$$

**Assumptions:** Annual rate of stent thrombosis (ST) during 12 – 30 m (i.e. very late ST) = 0.5% for 12m DAPT and 0.225% for 30m DAPT; during 30 –33 m during 30 –33 m hazard ratio = 1.

# Benjamini-Hochberg Assumptions

- 1:1 randomized treatment allocation
- 12m vs 30m treatment with DAPT
- 12-33m analysis period
  
- Lost to follow-up following rate = 3% after randomization

12,196 patients randomized at 12 months post-procedure will yield at least 80% power that the study has statistically met its objective under the above assumptions (power ranges from approximately 80% to 90% depending on correlation of outcomes). Thus, the number to be enrolled at time of stent implantation is approximately  $12,196/.8$  or 15,245 DES subjects.

# Benjamini-Hochberg Approach

- Benjamini-Hochberg approach has been successfully employed to allow two co-primary endpoints in clinical trials of cardiac devices
- Familywise error rate is controlled at the 0.05 level
  - Each null hypothesis needs to be rejected at the 0.05 level, or if not, at least one needs to be rejected at the 0.025 level, for the study to have statistically met its objective
  - A positive study will signify that 30m of DAPT reduces ST, MACCE or both compared with 12m after DES in subjects without absolute contraindications or indications for >12m of therapy
  - If both endpoints are negative, the confidence limits of the treatment difference will be reported so that the level of certainty can be interpreted by clinicians

# BMS comparison to DES

- If DES 12 vs 30m study is positive, it will be important to distinguish whether this effect is DES specific.
- Main study will allow operator selection of stent type
- Powered comparison of BMS vs DES on 12-33 m ST and MACCE rates will be made to determine non-inferiority of DES after propensity score adjustment for patient and procedure characteristics and treatments (including duration of DAPT).

# DAPT Total Study Enrollment

DES subjects randomized at 12m = 15,245 (74%)

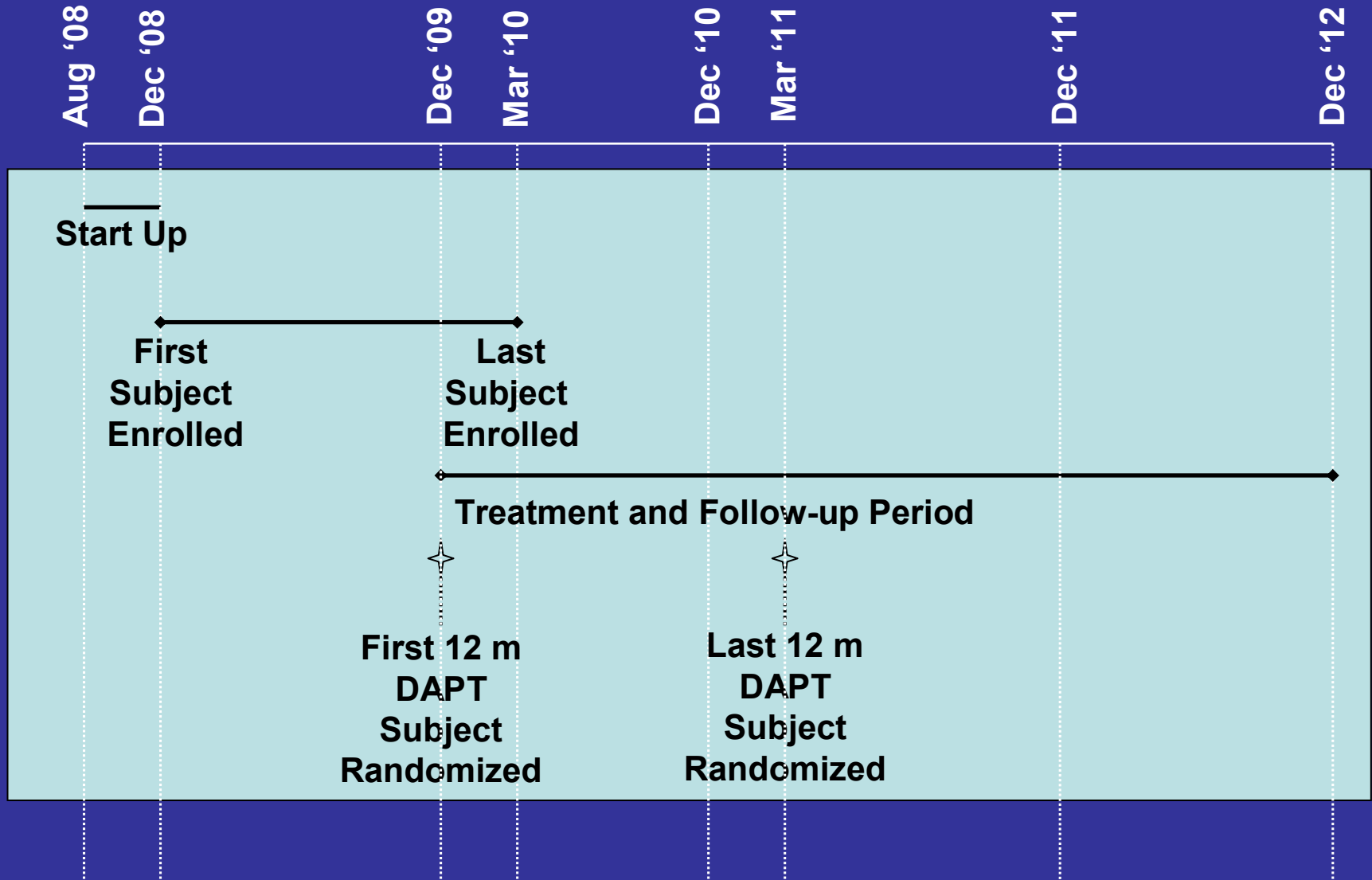
BMS subjects randomized at 12m = 5,400 (26%)

Total enrollment at time 0 = 20,645

# Drug Distribution and Compliance

- Drug to be open label until randomization
- Either clopidogrel or prasugrel (pending approval) will be included
- After randomization, drug + placebo will be distributed
- Unused drug will be returned and counted
- Analysis of patient reported, and medication compliance will be recorded with reasons and dates of interruption
- “On treatment” secondary analysis will be performed
- Sensitivity analysis of effect of drug-noncompliance will be performed

# Study Timeline



# Study Organization

**Study and IDE Sponsor:  
Harvard Clinical Research Institute**

**Principle Investigator: Laura Mauri  
Co- Principle Investigator: Dean Kereiakes**

**Data Management and US Safety: HCRI, Donald  
Cutlip, Executive Director of Clinical Investigation**

**Regulatory Advisor: CardioMed Device Consultants**

**OUS Safety: Quintiles**

**Independent CEC to adjudicate all events post  
randomization**

**Independent DSMB to monitor safety and  
enrollment**

# Conclusion

Given the likelihood that the DAPT study may affect changes in practice guidelines and DES labeling and impact patient care broadly, several principles are required

- Conclusive study design, whether negative or positive
- High level of integrity and unbiased nature of data collection, analysis, and presentation
- Broad participation of interventional cardiology community