Beijing,China 2009

# I-LOVE-IT – A Prospective, Multicenter Clinical Trial of TIVOLI™ Bioabsorbable Polymer Based Sirolimus-Eluting vs. ENDEAVOR™ Zotarolimus-Eluting Stent in Patients with Coronary Artery Disease: 8-Month Angiographic and 1-Year Clinical Follow-Up Results

**Run-Lin Gao, MD, FACC**

On Behalf of I-LOVE-IT Trial Investigators

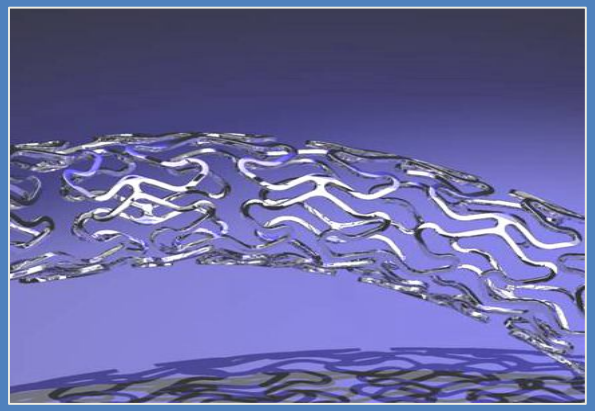
Beijing,China 2009

# Disclosure: The study was sponsored by Esan Corp.,Beijing, China

Beijing,China 2009

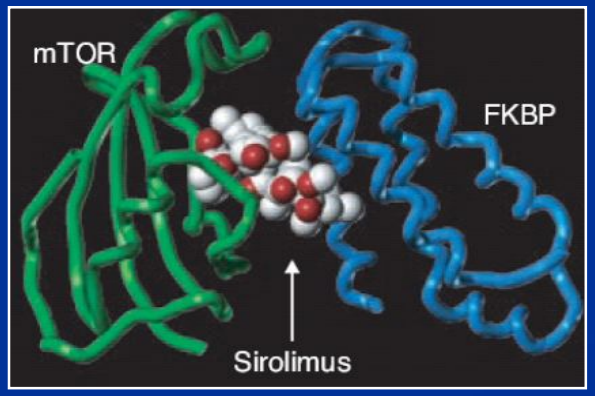
# TIVOLI DES Components

## Co-Cr stent

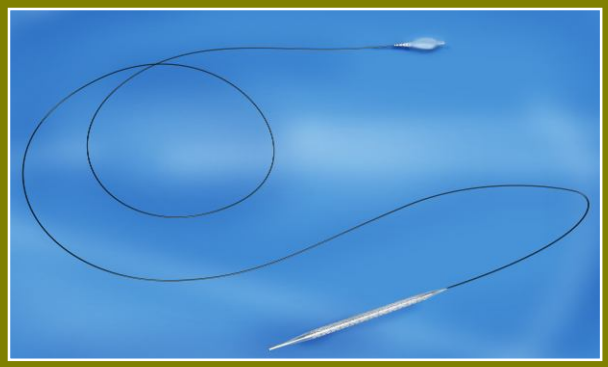


## PLGA Bioabsorbable Coating

## Sirolimus



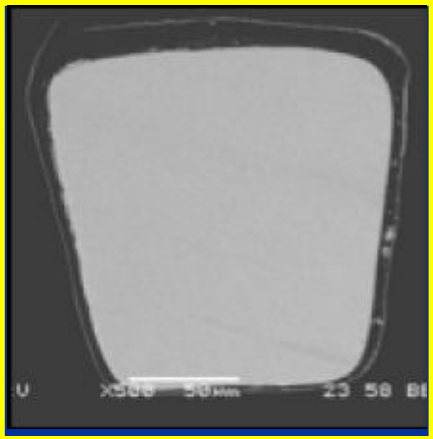
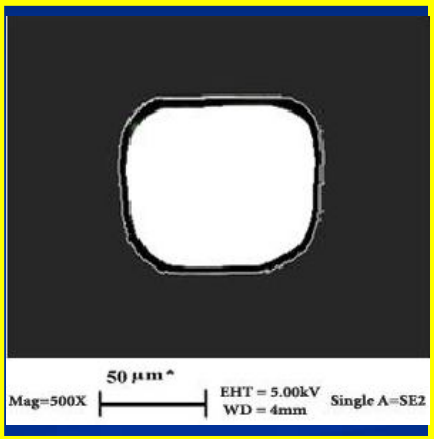

## Stent Delivery System



tmd.com

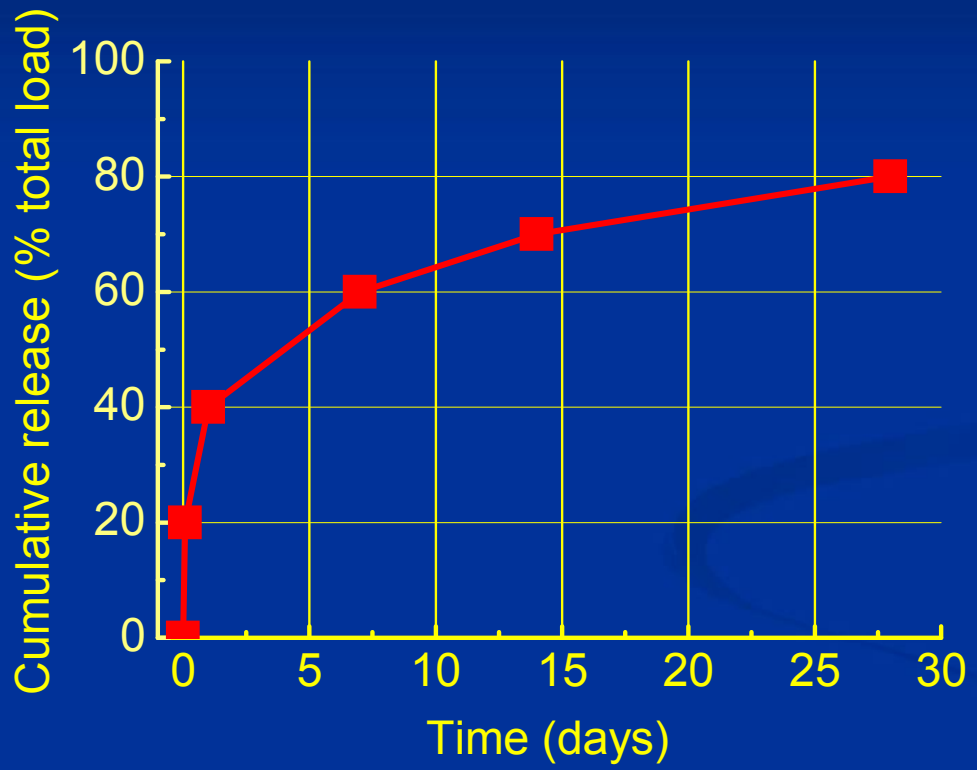
Beijing,China 2009

# Comparison of Strut and Coating Thickness

| Cypher® | Endeavor™ | Xience™ V | Tivoli™ |
|---|---|---|---|
|  | | |   |
| Strut Thickness | Strut Thickness | Strut Thickness | Strut Thickness |
| 140 um | 91 um | 81 um | 80 um |
| Polymer Thickness | Polymer Thickness | Polymer Thickness | Polymer Thickness |
| 12.6 um | 5.3 um | 7.6 um | 5.5 um |
| PEVA+PBMA | PC | Fluoropolymer | PLGA |
| Sirolimus | Zotarolimus | Everolimus | Sirolimus |

Beijing,China 2009

# Drug Eluting Kinetics



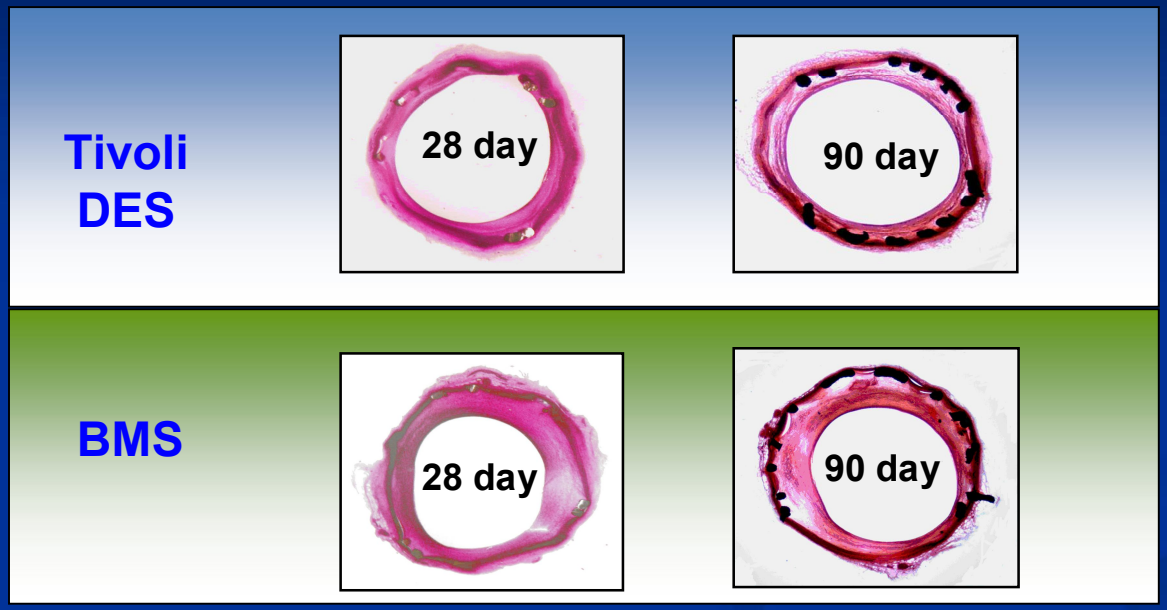

**8 ug Sirolimus per mm stent length**

www.citmd.com

Beijing,China 2009

# TIVOLI Animal Study

## *28 days to 90 days*




| Time | Stents | Lumen area ($mm^2$) | Internal elastic lamina area ($mm^2$) | Neointimal area ($mm^2$) | Stenosis(%) |
|---|---|---|---|---|---|
| 28 days | BMS | 2.65±1.03 | 4.53±0.36 | 1.88±0.71 | 42.67%±17.14% |
| | POS | 2.19±0.70 | 3.89±0.36 | 1.71±0.69 | 43.63%±17.54% |
| | DES | 3.19±0.76 | 4.09±0.55 | 0.90±0.40 | 22.83%±12.12%* |
| 90 days | BMS | 2.75±0.48 | 4.79±0.60 | 1.90±0.55 | 40.00%±11.98% |
| | POS | 2.39±0.70 | 4.57±0.62 | 2.17±0.73 | 47.83%±16.77% |
| | DES | 3.50±0.48 | 4.81±0.15 | 1.33±0.54 | 27.33%±10.69%# |

* At 28-day, the DES compared with BMS resulted in significantly less area stenosis(%), P=0.015

# At 90-day, the DES tended to show less area stenosis (%) compared with BMS, P=0.128

www.citmd.com

Beijing,China 2009

# I-LOVE-IT

**A Prospective, Multicenter Clinical Trial of TIVOLI™ Bioabsorbable Polymer Based Sirolimus-Eluting vs. ENDEAVOR™ Zotarolimus-Eluting Stent in Patients with Coronary Artery Disease: 8-Month Angiographic and 1-Year Clinical Follow-Up Results**

## Objective:

- To demonstrate non-inferiority of Tivoli to the Endeavor drug eluting stent in subjects with a maximum of two *de novo* native coronary artery lesions (lesion length ⩽ 40mm; RVD 2.25-4.0mm)

Beijing,China 2009

# Study Design

Prospective, Parallel, Controlled, Multi-Center Clinical Study
Lesions ≤ 40 mm in length, 2.25 – 4.0 mm diameter
324 Patients at 12 Centers

Tivoli™
Sirolimus-eluting Stent
N = 168

Endeavor ™ Coronary Stent
(Control Group)
N = 156

**Antiplatelet Therapy:**

Clopidogrel 300 mg loading dose, 75 mg QD at least 6 months
Aspirin 100 -300mg QD for 3 months, and daily ASA indefinitely

Beijing,China 2009

# I-LOVE-IT: Inclusion and Exclusion Criteria

## Key Inclusion

- Age 18-75yrs
- Target lesion no. <=2
- Lesion length <=40mm
- RVD 2.25mm~4.0mm
- DS% >=70% by visual estimation

## Key Exclusion

- CTO (TIMI 0), LM, ostial lesion, SVG, bifurcation (side branch RVD>=2.5mm), ISR
- AMI within 1 week
- Thrombus-containing lesion
- NYHA >=III or LVEF<40%
- Prior stenting in target vessel or in any vessel within 6mo

Beijing,China 2009

# I-LOVE-IT

- **Primary Endpoint**
  - --- Angiographic in-stent late loss at 240-day
- **Secondary Endpoints**
  - Angiographic in-stent and in-segment binary restenosis at 240-day
  - Clinical (MACE, TLR, MI, cardiac death, stent thrombosis) outcomes at 1-year
  - Device and procedure success

www.citmd.com

Beijing,China 2009

# I-LOVE-IT

- **Statistical Assumptions**
  - Two-sided 95% upper confidence bound for the difference in means between treatment groups
  - Margin of difference to support non-inferiority was 0.20 mm
  - SD = 0.46*
  - Alpha = 0.05
  - power = 80%
- **168 patients needed**
- **A total 320 patients needed due to an assumed 45% lost to angiographic follow-up**

** Fajadet J, Wijns W, Laarman GJ, Kuck KH, Ormiston J, Munzel T, Popma JJ, Fitzgerald PJ, Bonan R, Kuntz RE. Circulation. 2006;114(8):798-806.*

Beijing,China 2009

# I-LOVE-IT

**PI Prof. Runlin Gao**
Cardiovascular Institute and Fu Wai Hospital, Chinese Academy of Medical Sciences

**QCA Core Lab Bo Xu, Director**
Cardiovascular Interventional Center, Fu Wai Hospital, Chinese Academy of Medical Sciences

**Data Management Prof. Wei Li**
National Center for Cardiovascular Diseases, China

**CRO Beijing DMS Pharma Ltd.**

**Clinical Events Committee**
Prof. Wenling Zhu, Peking Union Medical College
Prof. Weimin Wang, Peking University People's Hospital
Prof. ShuYang Zhang, Peking Union Medical College

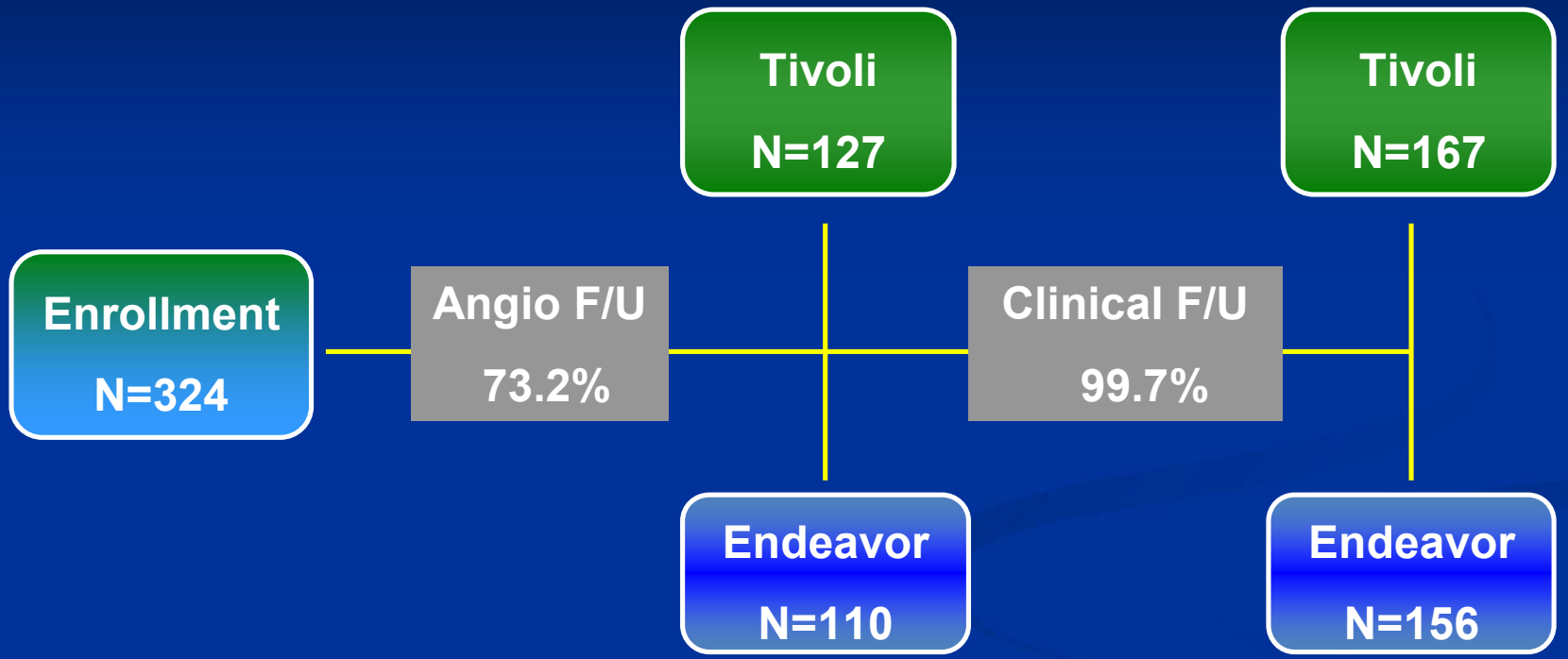
Beijing,China 2009

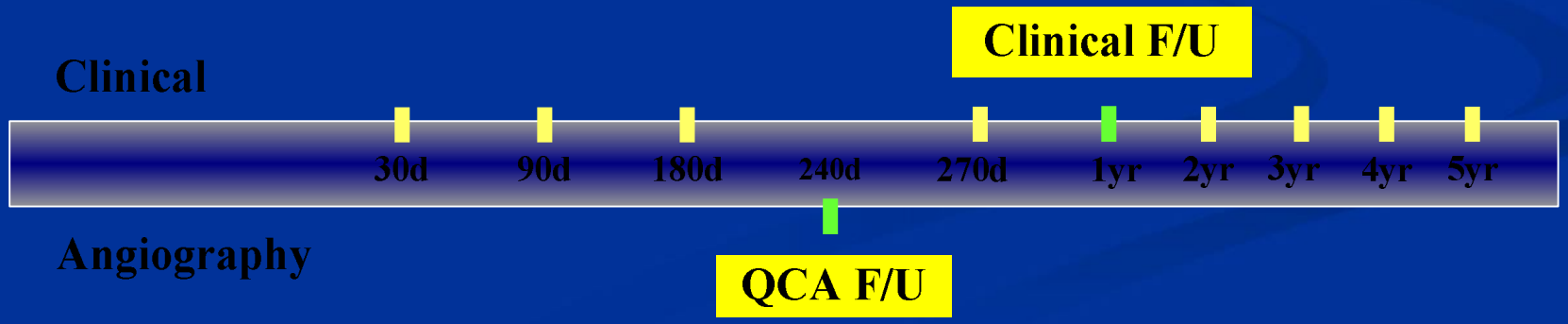
# Study Investigators

| Center | Investigator | Hospital |
|---|---|---|
| 01 | Yuejin Yang | Cardiovas. Inst.& Fuwai Hospital, Chinese Acad. of Med. Sci. |
| 02 | Shuzheng Lv | Anzhen Hospital, Capital University of Medical Sciences |
| 03 | Yong Huo | Peking University First Hospital |
| 04 | Lefeng Wang | Beijing Chao-Yang Hospital, Capital Univ. of Medical Sciences |
| 05 | Lei Wang | Beijing Friendship Hospital, Capital Univ. of Medical Sciences |
| 06 | Tingshu Yang | The General Hospital of the People's Liberation Army |
| 07 | Yong Wang | China-Japan friendship Hospital |
| 08 | Weimin Li | The First Clinical College of Herbin Medical University |
| 09 | Yaling Han | Shenyang Northern Hospital |
| 10 | Haichang Wang | Xijing Hospital, the Fourth Military Medical University |
| 11 | Junbo Ge | Zhongshan Hospital, Fudan University |
| 12 | Jiyan Chen | Guangdong Cardiov. Institute, Guangdong General Hospital |

Beijing,China 2009

# Trial Follow Up Schedule




www.citmd.com

Beijing,China 2009

# Baseline Characteristics

| Characteristic | Tivoli N=168 pts | Endeavor N=156 pts | P |
|---|---|---|---|
| Age, yr | 57.0±11.4 | 60.4±10.5 | 0.0054 |
| Male sex, % | 70.2 | 71.2 | 0.8564 |
| Prior MI, % | 31.6 | 17.3 | 0.0028 |
| Prior PCI, % | 11.3 | 10.3 | 0.7601 |
| Prior CABG, % | 0.6 | 0.6 | 1.0000 |
| Diabetes mellitus, % | 26.2 | 25.6 | 0.9102 |
| Hypertension, % | 54.8 | 57.0 | 0.6784 |
| Hypercholesterolemia, % | 20.8 | 23.1 | 0.6258 |
| Current smoker, % | 46.4 | 43.6 | 0.8471 |
| Unstable angina, % | 80.4 | 70.5 | 0.0096 |
| Left ventricular ejection fraction, % | 61.6±8.9 | 65.5±9.0 | 0.0003 |
| Lesion number/ patient | 1.43±0.50 | 1.27±0.44 | 0.0018 |

www.cirmd.com

Beijing,China 2009

# Baseline Vessel and Lesion Characteristics

| Characteristic | Tivoli N=216 lesions | Endeavor N= 186 lesions | P |
|---|---|---|---|
| Target vessel location, % | | | 0.9326 |
| LAD | 48.5 | 50.0 | |
| LCX | 21.4 | 21.6 | |
| RCA | 30.1 | 28.4 | |
| ACC/AHA, % | | | 0.7157 |
| A/B1 | 51.2 | 49.5 | |
| B2/C | 48.8 | 50.5 | |
| Pre-procedure QCA | | | |
| RVD, mm | 2.81±0.45 | 2.88±0.47 | 0.0953 |
| MLD, mm | 0.80±0.42 | 0.81±0.41 | 0.6906 |
| DS, % | 72.1±13.6 | 72.3±12.1 | 0.8393 |
| Lesion length, mm | 22.36±10.94 | 19.38±9.15 | 0.0028 |

www.citmd.com

Beijing,China 2009

# Post-Procedure Results

| Characteristic | Tivoli N=216 lesions | Endeavor N=186 lesions | P |
|---|---|---|---|
| Pre-dilatation, % | 57.0 | 62.2 | 0.2788 |
| Stent diameter , mm | 3.04±0.44 | 3.12±0.46 | 0.0352 |
| Stent length , mm | 29.18±12.88 | 24.11±9.84 | <0.0001 |
| Post-dilatation , % | 20.5 | 23.3 | 0.4555 |
| Device success , % | 100% | 100% | |
| Post-procedural QCA | | | |
| RVD , mm | 3.14±0.43 | 3.25±0.45 | 0.0102 |
| Minimum lumen diameter, mm | | | |
| In-stent | 2.68±0.40 | 2.82±0.43 | 0.0008 |
| In-segment | 2.40±0.46 | 2.42±0.51 | 0.6341 |
| Diameter stenosis, % | | | |
| In-stent | 14.6±4.4 | 13.3±4.3 | 0.0020 |
| In-segment | 24.2±8.1 | 26.2±8.4 | 0.0158 |
| Acute gain, mm | | | |
| In-stent | 1.88±0.41 | 2.01±0.42 | 0.0030 |
| In-segment | 1.60±0.44 | 1.61±0.45 | 0.8860 |

www.citmd.com

Beijing,China 2009

# I-LOVE-IT
# Primary Endpoint Results

## *240-day In-stent Late Loss*, mm*

**Diff [95% CI]**
**-0.23 [-0.32, -0.14],**
**P<0.0001**

**56% reduction**

***PRIMARY ENDPOINT MET!***

* Randomly select one lesion when more than one lesions involved.

www.citmd.com

Beijing,China 2009

# I-LOVE-IT

## Angiographic Results at 240-Day

### *240-days In-segment Late Loss*, mm*

Diff [95% CI]
-0.13 [-0.23, -0.02],
P=0.0083

**40% reduction**

* Randomly select one lesion when more than one lesions involved.

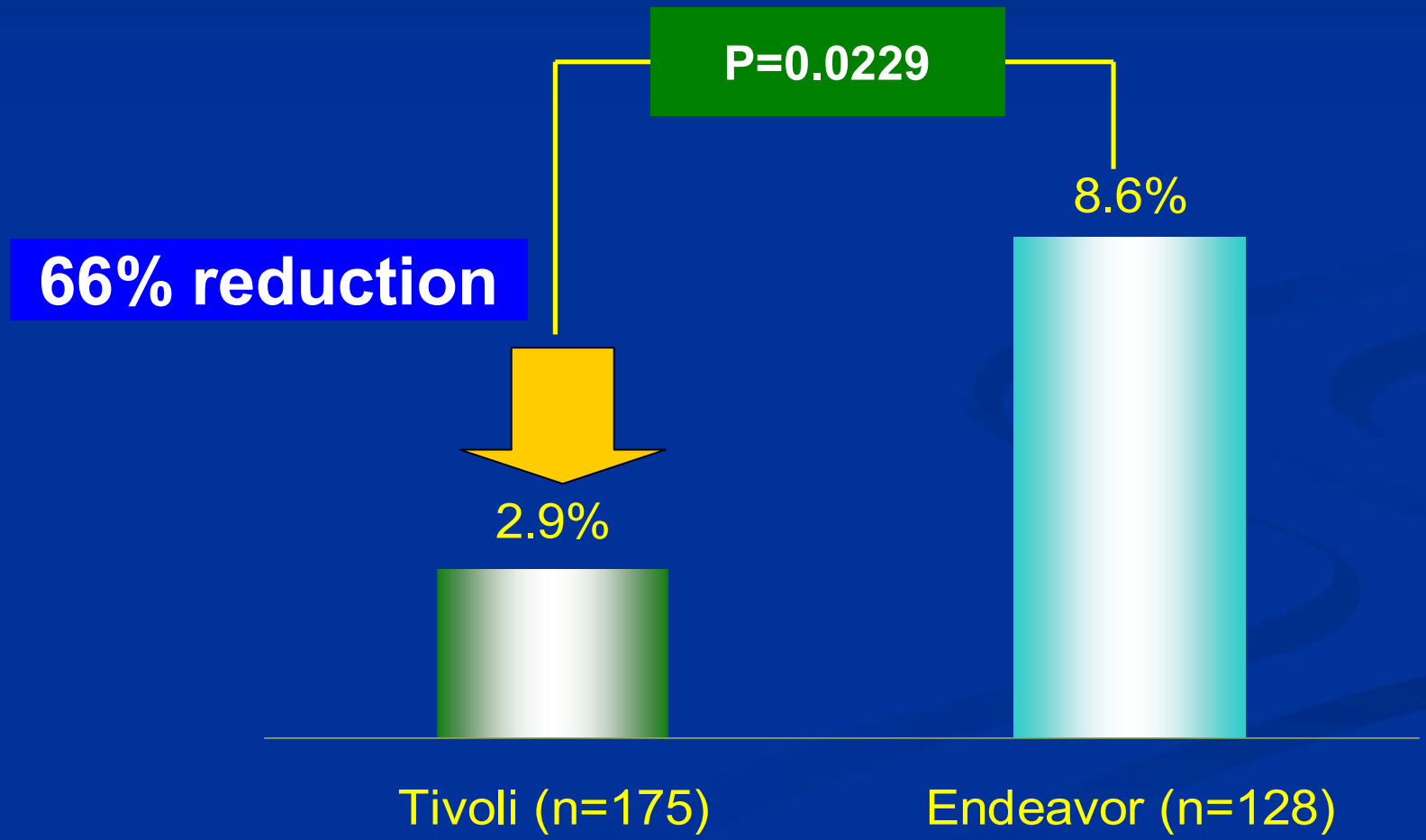
www.citmd.com

Beijing,China 2009

# I-LOVE-IT

## Angiographic Results at 240-Day

### *In-stent Angiographic Binary Restenosis*



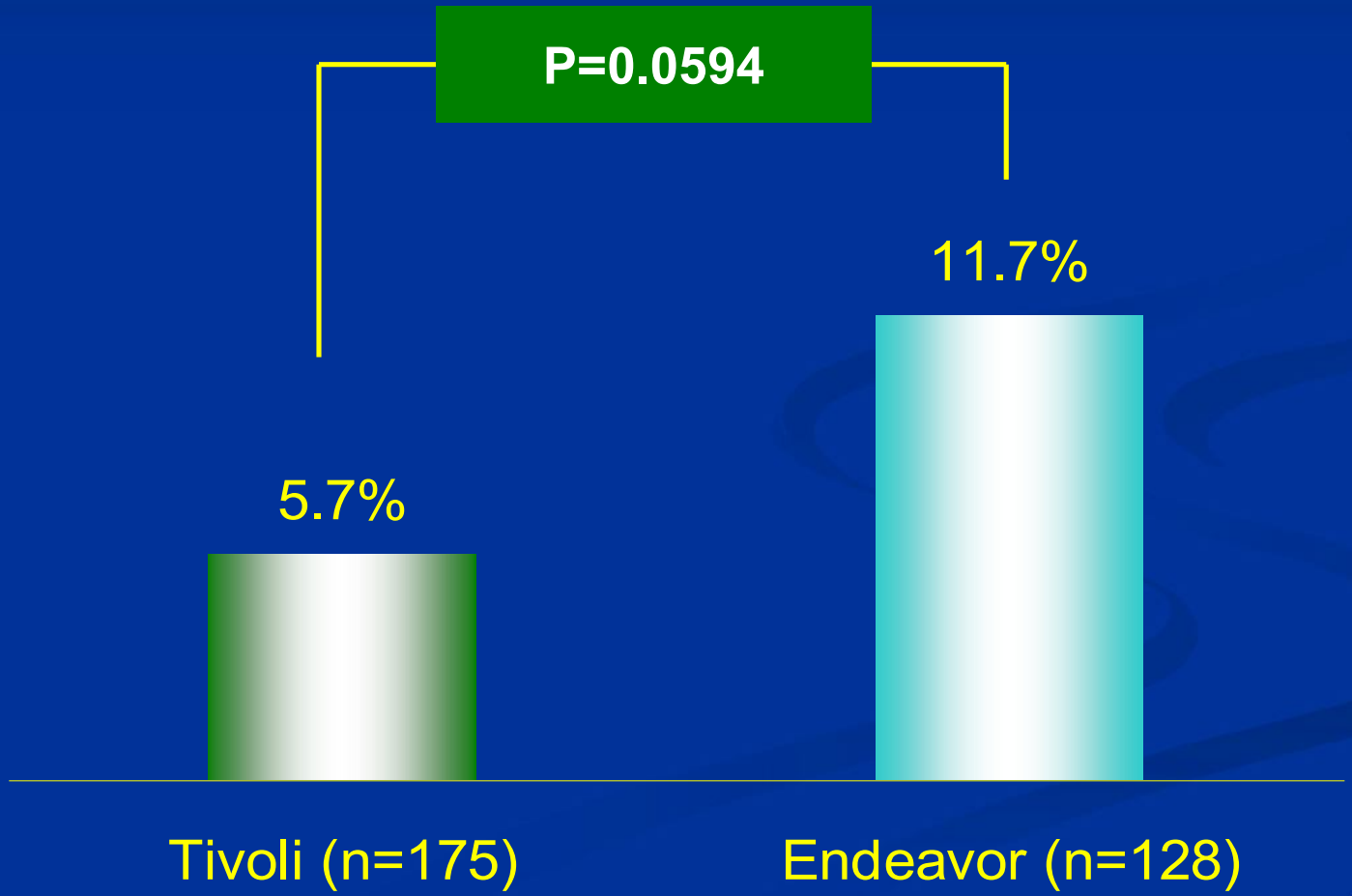

www.citmd.com

Beijing,China 2009

# I-LOVE-IT

## Angiographic Results at 240-Day

### *In-segment Angiographic Binary Restenosis*




www.citmd.com

Beijing,China 2009

# I-LOVE-IT

## Clinical Outcomes at One-Year

| Outcome | Tivoli N=168 pts | Endeavor N=156 pts | P |
|---|---|---|---|
| MACE, n (%) | 10(6.0) | 17(10.9) | 0.1424 |
| Death, n (%) | 0 | 0 | - |
| **Cardiac death, n (%)** | 0 | 0 | - |
| MI, n (%) | 4(2.4) | 2(1.3) | 0.6859 |
| Q wave | 1(0.6)* | 0 | 1.0000 |
| Non-Q wave | 3(1.8) | 2(1.3) | 1.0000 |
| TLR, n (%) | 7(4.2) | 15(9.6) | 0.0495 |
| Re-PCI | 7(4.2) | 15(9.6) | 0.0495 |
| CABG | 0 | 0 | 1.0000 |

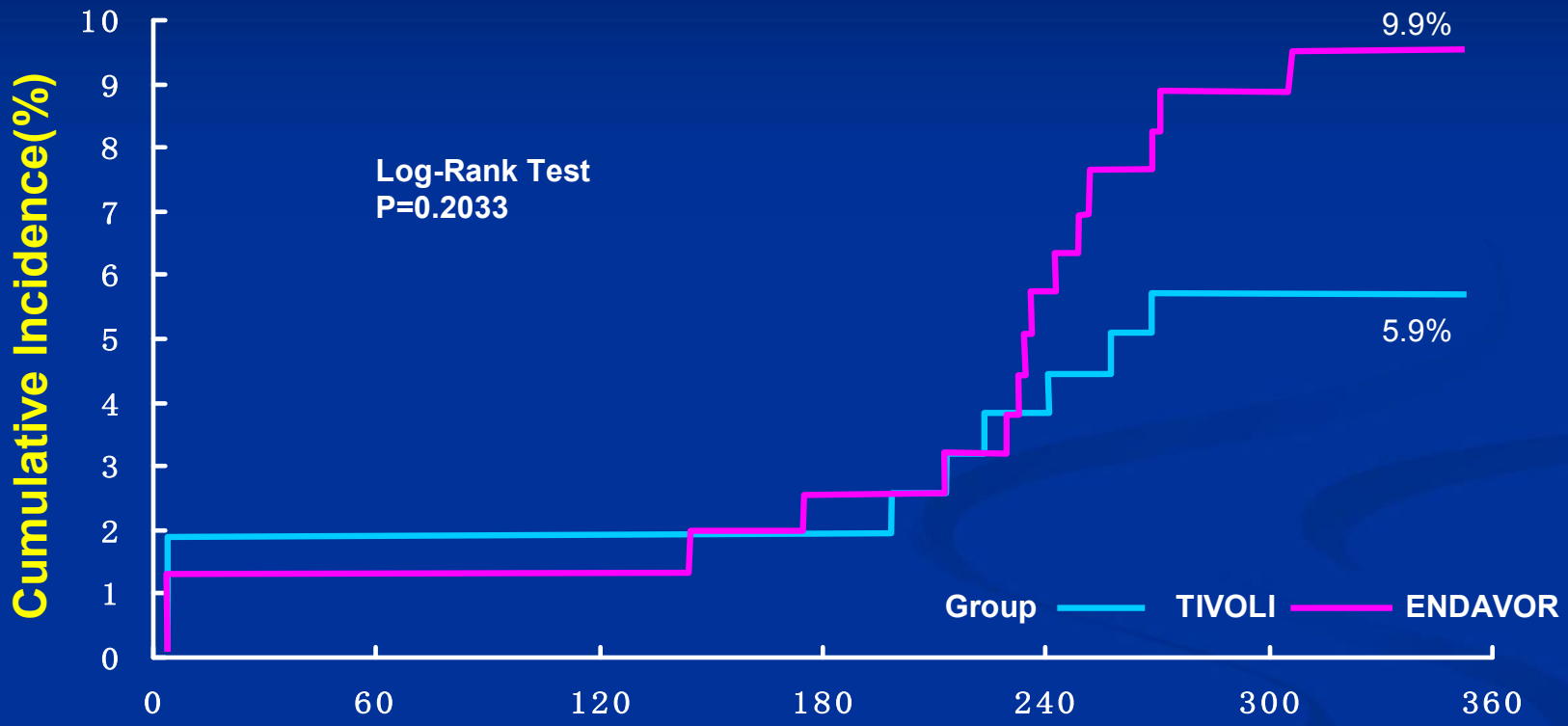
*** After 1 wk following the procedure, the patient stopped taking aspirin w/o permission for two wks due to a stomach disorder.**

www.citmd.com

Beijing,China 2009

# I-LOVE-IT

## One-Year Cumulative Incidence (MACE)




Time After Initial Procedure (days)

www.citmd.com

Beijing,China 2009

# Dual Antiplatelet Therapy

www.citmd.com

Beijing,China 2009

# I-LOVE-IT
## Stent Thrombosis at One-Year

| | Tivoli | Endeavor | P |
|---|---|---|---|
| **ARC definite/probable** | 1*/168 (0.6%) | 0/156 (0%) | - |
| **- Definite** | 1*/168 (0.6%) | 0/156 (0%) | - |
| **- Probable** | 0/168 (0%) | 0/156 (0%) | - |
| **- < 24 hours** | 0/168 (0%) | 0/156 (0%) | - |
| **- 24 hours - 30 days** | 1*/168 (0.6%) | 0/156 (0%) | - |
| **- > 30 days – 1 year** | 0/168 (0%) | 0/156 (0%) | - |

*** After 1 wk following the procedure, the patient stopped taking aspirin w/o permission for two wks due to a stomach disorder.**

www.citmd.com

Beijing,China 2009

# Tivoli Compared to Other DES

| | SIRIUS | TAXUS Ⅳ | ENDEAVOR Ⅱ | SPIRIT Ⅲ | I-LOVE-IT |
|---|---|---|---|---|---|
| DES | Cypher | Taxus | Endeavor | Xience V | Tivoli |
| Patients enrolled | 533 | 662 | 598 | 669 | 168 |
| RVD, mm | 2.80±0.47 | 2.75±0.47 | 2.74±0.48 | 2.77±0.45 | 2.81±0.45 |
| Lesion Length, mm | 14.4±5.8 | 13.4±6.3 | 14.1±5.6 | 14.7±5.6 | 22.36±10.94 |
| Angiographic F/U, day | 240 | 270 | 240 | 240 | 240 |
| In-stent binary restenosis, % | 3.2 | 5.5 | 9.4 | 2.3 | 2.9 |
| In-segment binary restenosis, % | 8.9 | 7.9 | 13.2 | 4.7 | 5.7 |
| In-stent late loss, mm | 0.17±0.45 | 0.39±0.50 | 0.61±0.46 | 0.16±0.41 | 0.25±0.33 |
| Clinical F/U, day | 270 | 270 | 270 | 360 | 360 |
| MACE，% | 7.1 | 8.5 | 7.3 | 6.0 | 6.0 |
| Cardiac death，% | 0.9 | 1.4 | 0.8 | 0.8 | 0 |
| MI，% | 2.8 | 3.5 | 2.7 | 2.8 | 2.4 |
| TLR，% | 4.1 | 3.0 | 4.6 | 3.4 | 4.2 |
| Stent thrombosis，% | 0.4 | 0.6 | 0.5 | 0.8 | 0.6 |

www.citmd.com

Beijing,China 2009

# Limitation

- This is a non-randomized trial, bias may exist; however, the baseline characteristics for both groups are comparable, Tivoli group had slightly unfavorable baseline characteristics such as lesion length.

- The TLR reported for this trial are “all TLR”, instead of “clinically driven TLR”,because of 8-month angiographic follow-up.

Beijing,China 2009

# Conclusion: I-LOVE-IT

- The data indicates that the TIVOLI™ stent was superior to the ENDEAVOR™ stent with respect to in-stent late loss at 8-month
- TIVOLI™ stent shows lower binary restenosis rate at 8-months
- TIVOLI™ stent is as safe as ENDEAVOR™ stent according to 1-year clinical results
- TIVOLI™ stent shows lower TLR at 1-year

www.citmd.com

Thank you