FIMA-DEFER Trial:

A Double-blind, Randomized Trial of Effect of Fimasartan for Modification of Atheroma Vulnerability in Deferred Coronary Disease

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The TCTAP 2018 Disclosure

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I have no financial conflicts of interest to disclose concerning the presentation

Background

- Fimasartan is a newly developed angiotensin II receptor blocker.
- ARB showed to decrease percent atheroma volume in a randomized trial (Hirohata et al., JACC, 2010).
- The effect of the ARB on the modification of plaque composition and stabilization has not been studied.

FIMA-DEFER Trial

Design

- DESIGN: a multi-center, prospective, double-blind, placebo-controlled, randomized trial
- OBJECTIVE: To compare the effect of Fimasartan on stabilizing the coronary plaque vulnerability
- PRINCIPAL INVESTIGATOR
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  Asan Medical Center, Seoul, Korea

Major Inclusion Criteria

- Clinical criteria

  1. Hypertension
  (SBP >140 or DBP >90 mmHg or on anti-hypertensive Rx)
  2. Age ≥ 18, <85 years old

- Anigiographic criteria

  1. Visually-estimated diameter stenosis 20~50%, or
  2. Visually-estimated DS > 50% without inducible ischemia
  (FFR ≥ 0.8 or Thallium SPECT (-) or TMT (-))

Major Exclusion Criteria

- Clinical criteria
  1. Planned PCI or CABG at the target vessel
  2. Congestive heart failure or LV EF < 40%
  3. CVA < 6 months
  4. Cr ≥ 1.5 mg/dl
  5. Planned major surgery
  6. Chronic systemic steroid therapy
  7. Malignancy within 3 years
  8. Allergy to ARB

Major Exclusion Criteria

- Angiographic Criteria
  1. Previous history of CABG or PCI
  2. LM disease > 50% diameter stenosis
  3. Reference vessel diameter < 2.75 or > 4.0 mm
  4. Unfavorable anatomy for intracoronary imaging
  5. Vessel with high distal embolic risk
  6. Culprit vessel of myocardial infarction

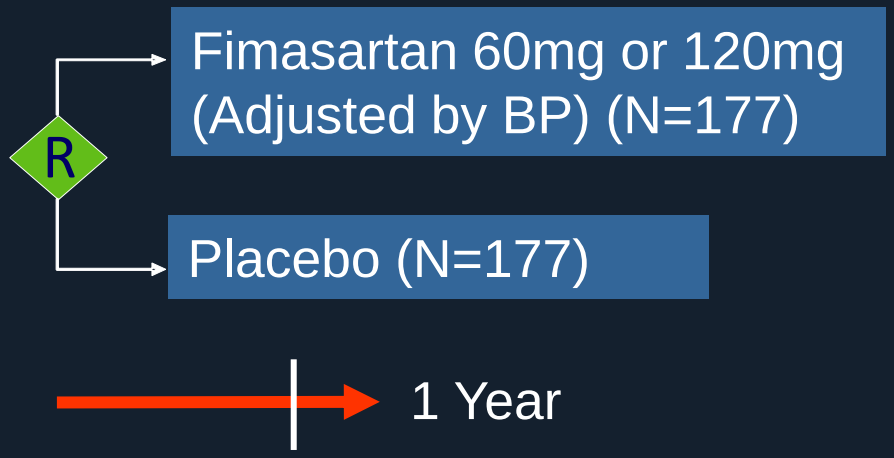
Study Design

Patients with
Deferred CAD with

1) Diameter stenosis 20~50%

OR

2) Diameter stenosis > 50% without inducible ischemia (FFR > 0.80)



Primary endpoint:
Change in %necrotic core (NC) volume of plaque by VH in the target segment at 1 year

Study Procedures (1)

- Patients were randomly assigned either to Fimasartan 60-120 mg or placebo as 1:1 ratio.
- In the Fimasartan group, Initial dose was started with 60mg qd. At 4 week follow-up, dose titration upto 120 mg qd was made if the patient was not hypotensive.
- If optimal BP is not achieved (SBP>140mmHg or DBP>90mmHg) with Fimasartan 120 mg qd, new anti-hypertensive drug was added.

Study Procedures (2)

- Drug compliance was checked at every visit.
- All subjects was asked to have angiography and VH-IVUS follow-up at 1 year.

Primary End Point

- Change in percent necrotic core (NC) volume by virtual histology in the target segment from baseline from baseline to 1 year follow-up

Original Power Calculation

Superiority Design for Primary Endpoint

- Assumed primary end point
  : 1% difference between two groups (SD 5%)
- A two-sided type I error rate : 0.05
- Power : 90%
- Dropout rate: 25%
- Assumed sample size: 354 patients (1:1 ratio)

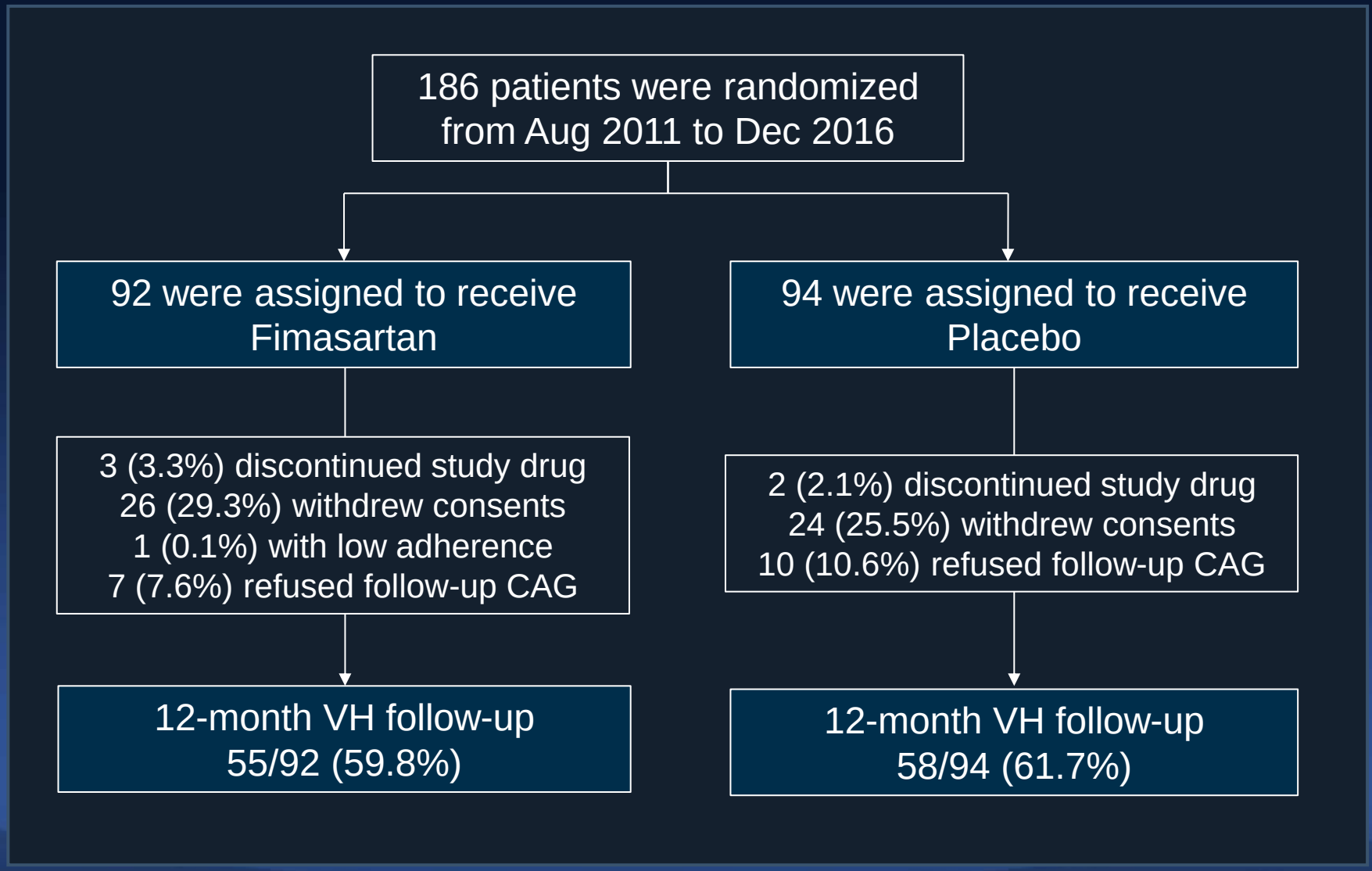
Premature Termination of Trial

- Because enrollment was slower than anticipated, enrollment was stopped in December 2016 as recommended by the data and safety monitoring board by which time 186 patients had been enrolled.
- The sponsor and study leadership were unaware of study results at the time of this decision.

Statistical Analysis

- Owing to premature termination of the study, this report provides descriptive information on primary and secondary study endpoints.
- Primary and second endpoints were analyzed in the per-protocol analysis set whose paired baseline and follow-up VH-IVUS data were available.
- Safety endpoints were analyzed in the full analysis set.
- Continuous variables were compared using unpaired Student t tests. Categorical variables were compared using chi-square statistics or the Fisher exact test.
- Changes in variables at 1-year follow-up from baseline were made using paired Student t tests for continuous and McNemar's test for categorical data.
- All P-values and CIs were two-sided. SPSS software version 21 was used for all statistical analyses.

Study Flow


186 patients were randomized from Aug 2011 to Dec 2016
92 were assigned to receive Fimasartan
94 were assigned to receive Placebo
3 (3.3%) discontinued study drug
26 (29.3%) withdrew consents
1 (0.1%) with low adherence
7 (7.6%) refused follow-up CAG
2 (2.1%) discontinued study drug
24 (25.5%) withdrew consents
10 (10.6%) refused follow-up CAG
12-month VH follow-up
55/92 (59.8%)
12-month VH follow-up
58/94 (61.7%)

Baseline Characteristics

	Fimasartan (N=55)	Placebo (N=58)	P value
Age (years)	62.6±8.7	63.1±8.5	0.79
Male sex	42 (76.4%)	37 (63.8%)	0.15
Body mass index (kg/m^2)	24.1±5.5	25.3±3.8	0.17
Hypertension	55 (100.0%)	58 (100.0%)	-
Diabetes	19 (34.5%)	18 (31.0%)	0.69
Current smoking	9 (16.4%)	17 (29.3%)	0.10
Hyperlipidemia	39 (70.9%)	46 (79.3%)	0.30
Previous MI	1 (1.8%)	0 (0.0%)	0.30
Previous CVA	1 (1.8%)	1 (1.7%)	0.97
Atrial fibrillation	0 (0%)	2 (3.4%)	0.17
Acute coronary syndrome	15 (27.3%)	18 (31.0%)	0.82
PCI at other vessels during index procedure	26 (47.3%)	30 (51.7%)	0.64

Baseline Laboratory Characteristics

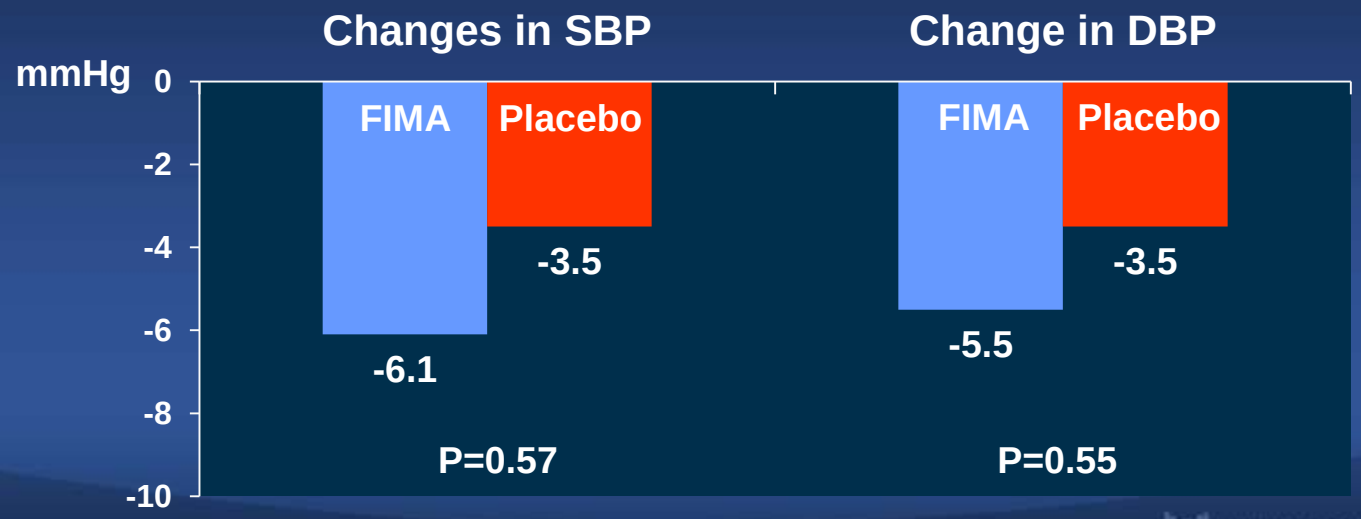
	Fimasartan (N=55)	Placebo (N=58)	P value
hs-CRP, mg/dL	0.23±0.42	0.35±0.83	0.41
Serum creatinine, mg/dL	0.90±0.20	0.92±0.22	0.68
BUN, mg/dL	15.4±3.6	15.9±3.6	0.50
Sodium, mEq/L	140.3±1.8	140.0±2.8	0.29
Potassium, mEq/L	4.2±0.3	4.3±0.5	0.78
Total cholesterol, mg/dL	156.1±32.7	163.3±39.2	0.29
LDL cholesterol, mg/Dl	92.0±28.6	99.4±33.0	0.22
HDL cholesterol, mg/dL	43.5±9.9	46.2±13.3	0.24
Triglycerides, mg/dL	137.4±61.0	155.0±119.8	0.35

Medication Profiles

	Fimasartan (N=55)	Placebo (N=58)	P value
Medication at discharge			
Aspirin	52 (94.5%)	52 (89.7%)	0.34
P2Y12 inhibitor	39 (70.9%)	33 (56.9%)	0.12
Statin	44 (91.7%)	45 (90.0%)	0.78
Beta-blockers	24 (52.2%)	22 (44.9%)	0.48
Calcium channel blockers	26 (57.8%)	24 (29.0%)	0.39
Medication at 12-months			
Aspirin	48 (87.3%)	49 (84.5%)	0.67
P2Y12 inhibitor	39 (70.9%)	33 (56.9%)	0.12
Statin	53 (96.4%)	54 (93.1%)	0.44
Beta-blockers	19 (34.5%)	27 (46.6%)	0.19
Calcium channel blockers	27 (49.1%)	36 (62.1%)	0.17
Compliance of the study drug	97.1±4.6	98.2±2.5	0.13

Serial Changes in Blood Pressure

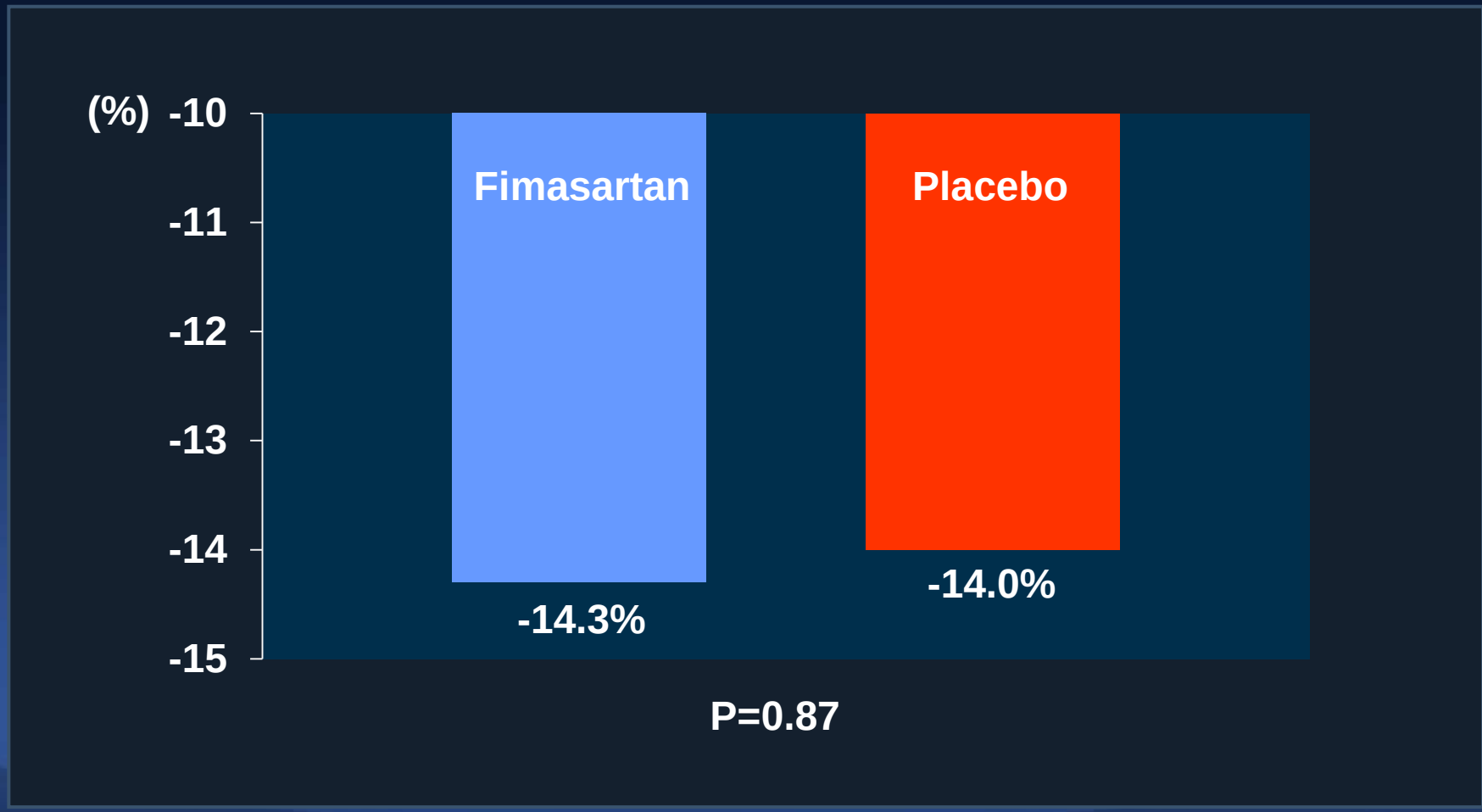
	Fimasartan (N=55)	Placebo (N=58)	P value
Baseline			
Systolic BP, mmHg	127.4±24.4	132.8±19.8	0.20
Diastolic BP, mmHg	75.9±18.9	78.9±12.0	0.32
12-month follow-up			
Systolic BP, mmHg	121.0±16.4	129.2±13.5	0.004
Diastolic BP, mmHg	70.3±10.7	75.4±11.6	0.02



Baseline IVUS & VH characteristics

	Fimasartan (N=55)	Placebo (N=58)	P value
Grayscale IVUS data			
Lesion length, mm	25.0±8.2	26.1±10.2	0.52
Total atheroma volume, mm^3	215.7±97.4	230.6±116.3	0.46
Percent atheroma volume, %	54.0±8.0	54.6±7.8	0.71
PAV at worst 10mm, %	58.8±9.1	59.9±8.5	0.51
MLA, mm^2	4.4±1.8	4.1±1.6	0.38
Plaque burden at MLA, %	67.6±9.4	69.3±8.4	0.31
VH-IVUS index segmental data			
Fibrous volume, %	58.3±8.4	57.3±7.6	0.54
Fibrofatty volume, %	18.1±10.0	17.8±9.3	0.84
Necrotic core volume, %	16.2±7.7	16.8±7.1	0.71
Dense calcium volume, %	7.4±4.8	8.2±5.8	0.40
Maximal %necrotic core, %	30.0±11.2	30.1±10.1	0.81
Worst plaque type			0.53
VH-TCFA	16 (29.1%)	15 (25.9%)	
Thick-cap fibroatheroma	38 (69.1%)	43 (74.1%)	
Pathological intimal thickening	1 (1.8%)	0	

Primary Endpoint
: Change in percent NC volume by VH in the target segment



Changes in Efficacy Endpoints

	Fimasartan (N=55)	Placebo (N=58)	P value
Change in MLA, mm^2	0.03±0.77	0.21±0.96	0.29
Change in normalized TAV, mm^3/m	0.10±0.98	-0.19±0.84	0.09
Change in PAV, %	-0.14±4.95	-1.05±3.40	0.26
Change in PAV at worst 10mm, %	0.12±5.0	-1.2±4.8	0.16
VH-IVUS segemental data			
Change in fibrous volume, %	-4.3±20.8	-10.1±24.0	0.18
Change in fibrofatty volume, %	-0.4±6.5	-1.5±5.5	0.14
Change in NC volume, %	-2.3±10.8	-0.7±13.4	0.48
Change in dense calcium volume, %	4.3±10.3	3.4±9.9	0.66
Worst plaque type			0.68
VH-TCFA	7 (12.7%)	9 (15.5%)	
Thick-cap fibroatheroma	41 (74.5%)	43 (74.1%)	
Pathological intimal thickening	5 (9.1%)	6 (10.3%)	
Fibrous	1 (1.8%)	0	

Changes in Laboratory Values

	Fimasartan (N=55)	Placebo (N=58)	P value
Change in hs-CRP, mg/Dl	-0.18±0.44	-0.27±0.88	0.54
Change in Serum creatinine, mg/dL	0.00±0.13	-0.02±0.18	0.56
Change in BUN, mg/dL	0.7±3.08	-1.0±3.8	0.03
Change in Sodium, mEq/L	-0.7±2.5	0.2±3.1	0.07
Change in Potassium, mEq/L	0.3±0.4	0.1±0.6	0.07
Change in Total cholesterol, mg/dL	-11.9±30.7	-25.7±37.8	0.04
Change in LDL cholesterol, mg/dL	4.6±55.0	-19.7±37.1	0.01
Change in HDL cholesterol, mg/dL	4.3±9.0	1.5±8.6	0.11
Change in Triglycerides, mg/dL	6.5±54.8	-17.9±111.1	0.17

Safety Endpoints in the ITT population

	Fimasartan (N=92)	Placebo (N=94)	P value
Death	0	0	-
Target vessel related MI	0	0	-
Target vessel revascularization	0	0	-
Cerebrovascular accident	0	0	-
Study drug-related adverse events			
Hypotension	2 (2.2%)	0	0.24
Dizziness or syncope	2 (2.2%)	1 (1.1%)	0.62

Conclusion

- The FIMA-DEFER the first randomized clinical trial to evaluate the effect of the ARB on the modification of coronary plaque composition.
- The ARB group did not show significant change of plaque composition and plaque vulnerability compared with placebo group.
- The power of this study was insufficient because of the premature termination and low angiographic follow-up rate.

Thank You !!

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