[JCR 2019]

Sex Difference of Long-term Outcomes on Coronary Microvascular Dysfunction

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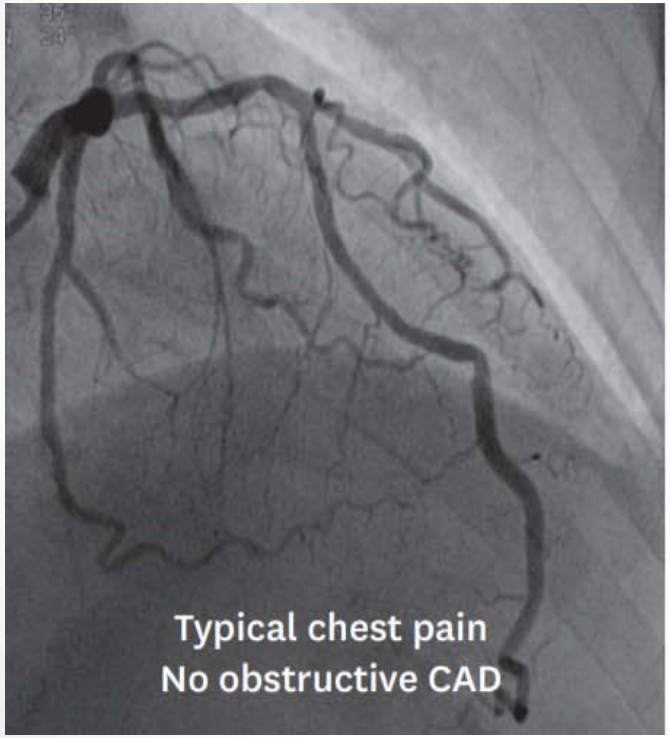
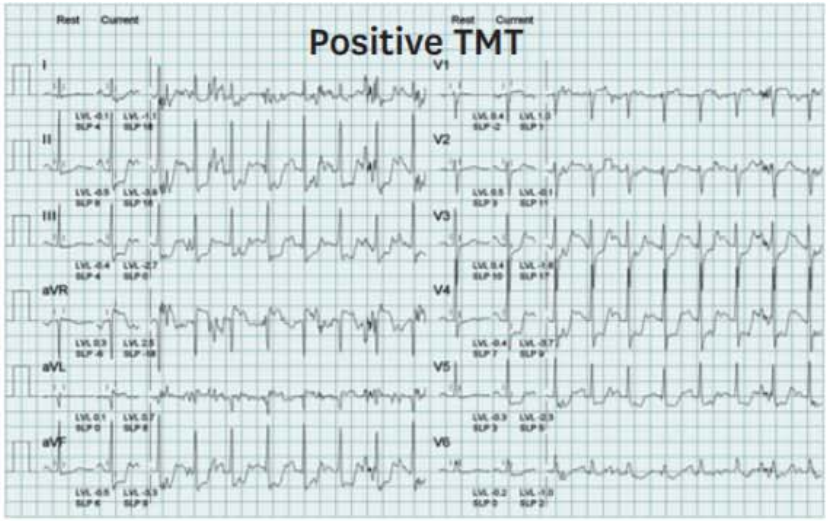
Dec 13, 2019

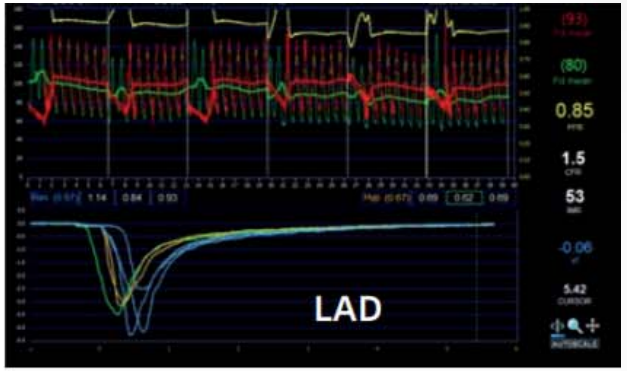
Background

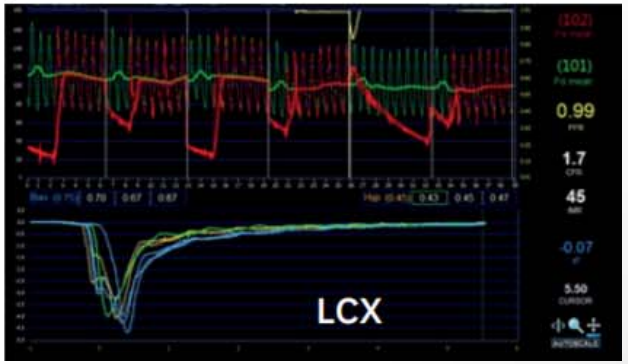
- **Patient with Microvascular Disease**





Chest pain from stage 3
Horizontal ST depression from stage 3
Duke score: –5 (moderate risk)





Korean Circ J. 2018 Mar;48(3):179-190.

Background

- **Angina with Non-obstructive Coronary Artery**
  - More common in women
  - Prognosis is not benign
  - Coronary micro-circulatory disease?

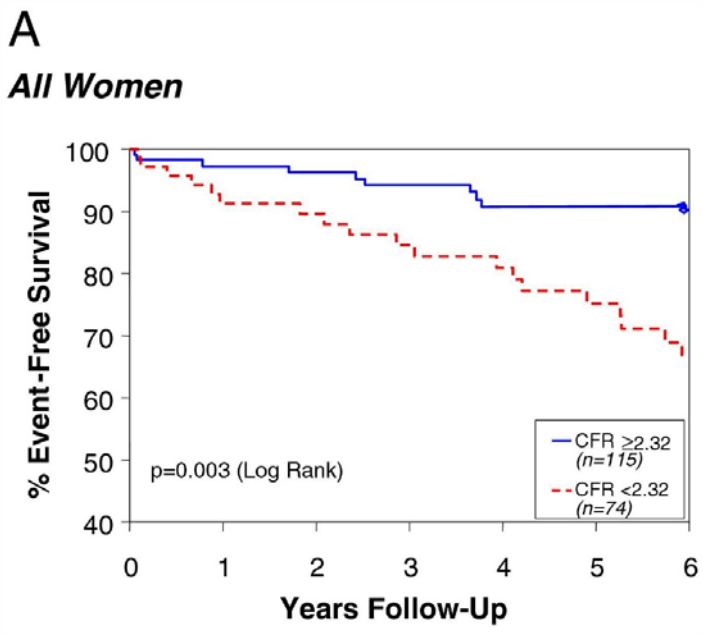
Table. Prevalence of "Normal" and Nonobstructive Coronary Arteries in Women Compared With Men

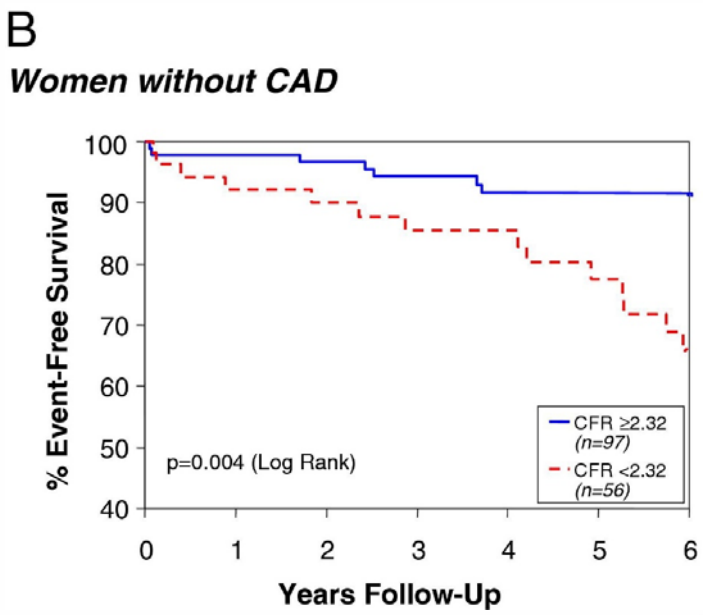
	No./Total (%)		
	Women	Men	*P* Value
Acute coronary syndrome			
GUSTO[2]	343/1768 (19.4)	394/4638 (8.4)	<.001
TIMI 18[3]	95/555 (17)	99/1091 (9)	<.001
Unstable angina[2]	252/826 (30.5)	220/1580 (13.9)	<.001
TIMI IIIa[6]	30/113 (26.5)	27/278 (8.3)	<.001
MI without ST-segment elevation[2]	41/450 (9.1)	55/1299 (4.2)	.001
MI with ST-segment elevation[2]	50/492 (10.2)	119/1759 (6.8)	.02

JAMA. 2005;293:477-484

Background

- **CFR for non-obstructive CAD in women**
  - Could predict major adverse outcomes (Death, MI, stroke, or hospital stay for HF)
  - 189 women, 5.4 years F/U

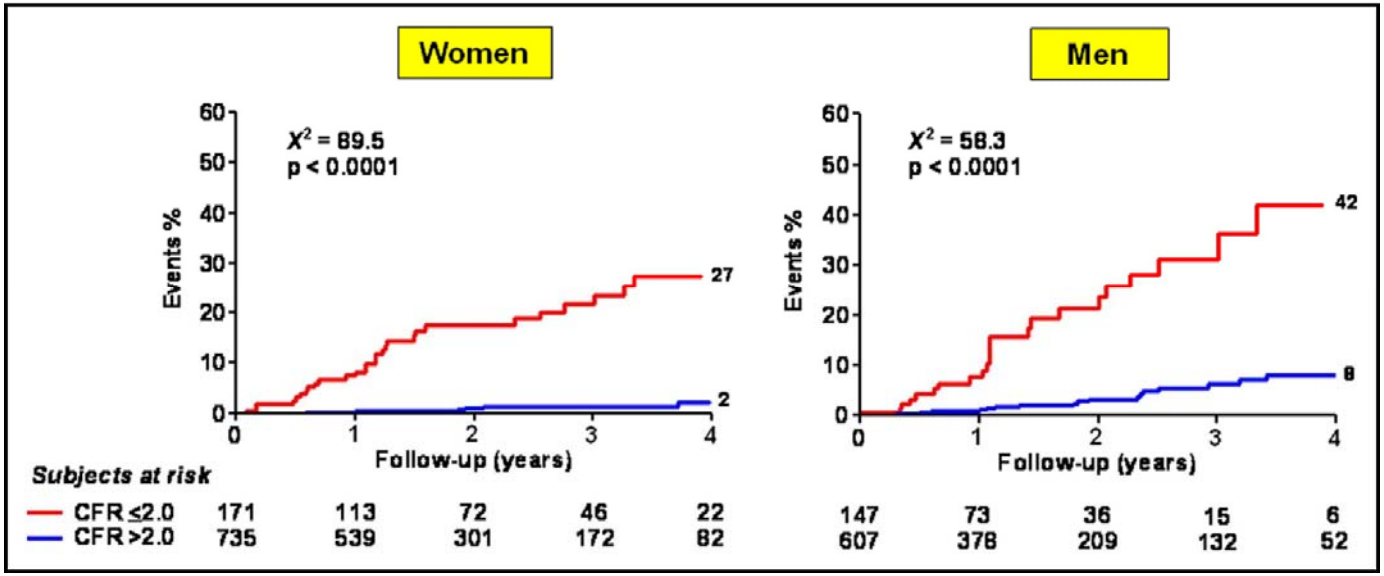




J Am Coll Cardiol 2010;55:2825–32

Background

- **CFR with chest pain syndrome and normal stress echoCG**
  - LAD only
  - 1,660 patients (906 women, 754 men), 4 years



Am J Cardiol 2010;106: 1703–1708

Purpose

- Limited data on the use of CFR and IMR as measures of the coronary microvasculature between women and men.
- CFR is affected not only by microvascular function, but also epicardial flow.
- In contrast, IMR is a direct measure of the microcirculation which is independent of variations in hemodynamic state.

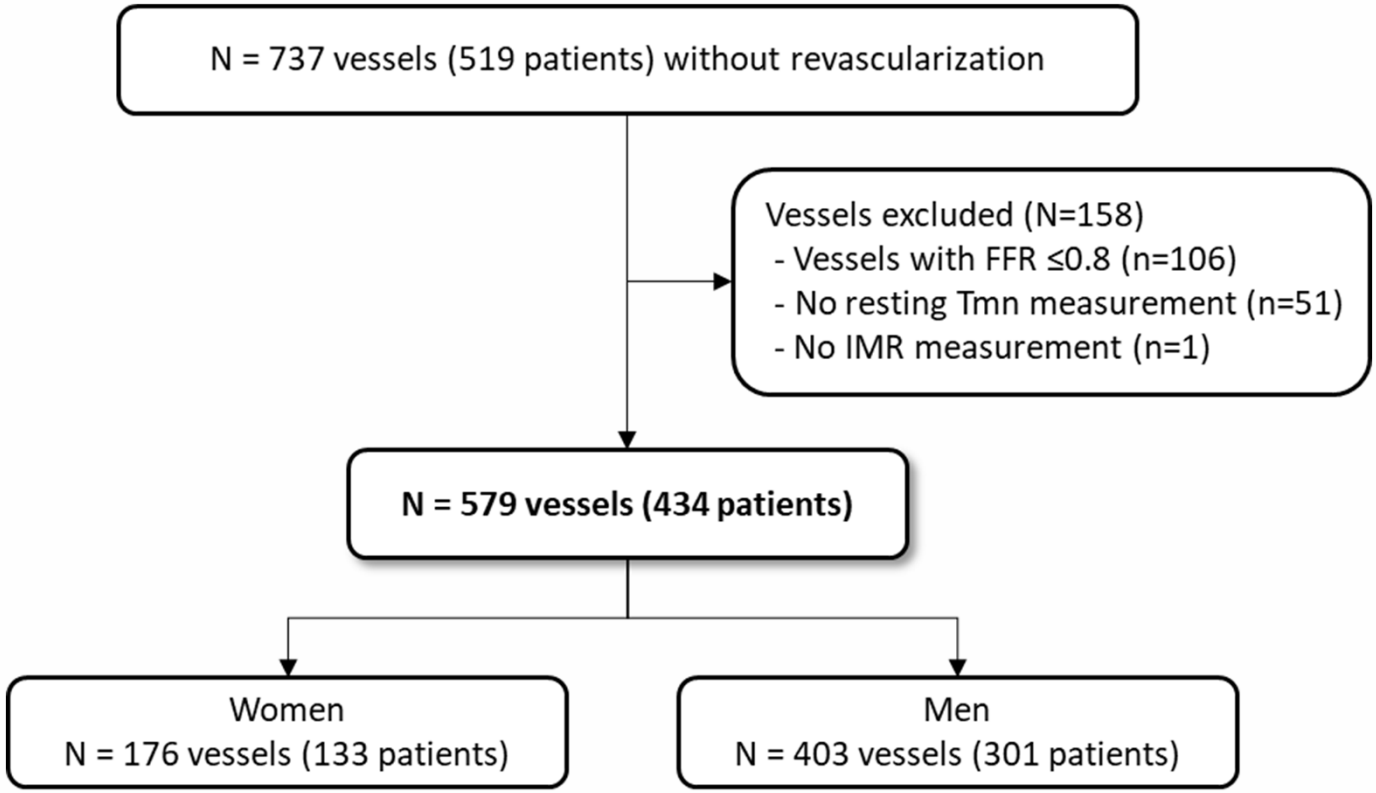
Sex difference in microvascular dysfunction and its effect on long-term outcomes?

Method

- **Patient selection**
  - Consecutive patients who underwent clinically indicated invasive coronary angiography and measurements of CFR, IMR and FFR in at least 1 coronary artery were prospectively enrolled.
  - 5 University Hospitals in Korea
  - Patients with hemodynamic instability, LV dysfunction, or a culprit vessel of acute coronary syndrome were excluded.
  - Vessels with FFR ≤0.80 despite of the absence of angiographic obstructive disease were also excluded.

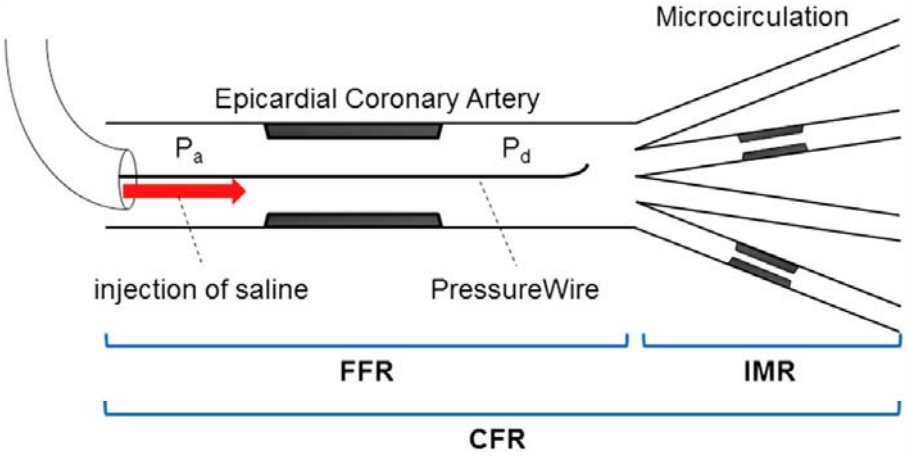
- **Primary endpoint**
  - MACE (a composite of cardiac death, MI, or revascularization) at 5 years

Method


N = 737 vessels (519 patients) without revascularization
Vessels excluded (N=158)
- Vessels with FFR ≤0.8 (n=106)
- No resting Tmn measurement (n=51)
- No IMR measurement (n=1)
N = 579 vessels (434 patients)
Women
N = 176 vessels (133 patients)
Men
N = 403 vessels (301 patients)

Method

- **Physiological assessment**
  - Single coronary pressure wire



- **FFR** $=P_d/P_a$ at maximal hyperemia
- **CFR** =hyperemic coronary flow ÷ resting coronary flow
  =1/hyperemic T_{mn} ÷ 1/resting T_{mn}
  =resting T_{mn}/hyperemic T_{mn}
- **IMR** $=P_d$ at maximal hyperemia ÷ 1/hyperemic T_{mn}
  $=P_d$ at maximal hyperemia × hyperemic T_{mn}

(T_{mn}: an inverse correlate to absolute coronary flow)

JACC Cardiovasc Interv. 2015;8:1433-1441

Method

- **Lesion classification**
  - Vessel-specific CMD: CFR ≤2.0 or IMR ≥23.
  - Subdivided CFR into resting flow and hyperemic flow using the median rTmn and hTmn.
  - Subdivided lesions into 4 groups according to sex and each coronary physiologic index.
  - Median values were used as cutoff values for rTmn (0.72) and hTmn (0.22).

Results

- **Patient clinical characteristics**

	Total	Women	Men	p value
Per-patient analysis	n = 434	n = 133	n = 301	
General characteristics				
Age, years	61.2 ± 10.4	62.7 ± 10.1	60.5 ± 10.4	0.037
Body mass index, kg/m2	24.5 ± 2.9	24.7 ± 3.1	24.4 ± 2.7	0.434
Ejection fraction, %	62.4 ± 9.0	64.5 ± 7.3	61.5 ± 9.6	0.002
Cardiovascular risk factors				
Hypertension	249 (57.4)	77 (57.9)	172 (57.1)	0.884
Diabetes mellitus	121 (27.9)	36 (27.1)	85 (28.2)	0.802
Hypercholesterolemia	261 (60.1)	70 (52.6)	191 (63.5)	0.034
Current smoker	80 (18.4)	4 (3.0)	76 (25.2)	<0.001
Family history of CAD	70 (16.1)	21 (15.8)	49 (16.3)	0.898
Previous PCI	122 (28.1)	27 (20.3)	95 (31.6)	0.016
Clinical presentation				0.703
Stable angina	361 (83.2)	112 (84.2)	249 (82.7)	
Unstable angina/NSTEMI	73 (16.8)	21 (15.8)	52 (17.3)	
Severity of CAD				
Multivessel disease	190 (43.8)	42 (31.6)	148 (49.2)	0.001
SYNTAX score	6.0 [0.0-12.0]	2.0 [0.0-9.0]	7.0 [2.0-13.0]	<0.001

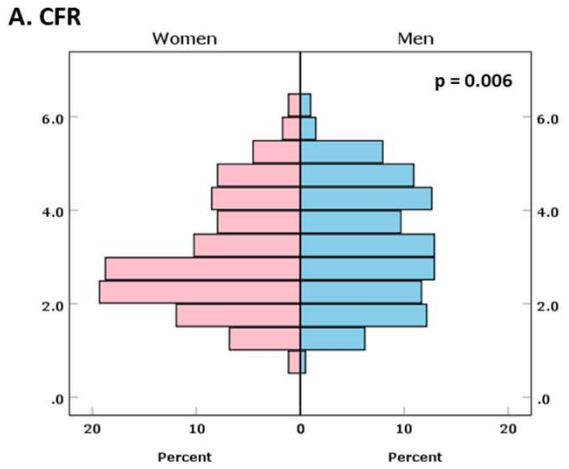
Results

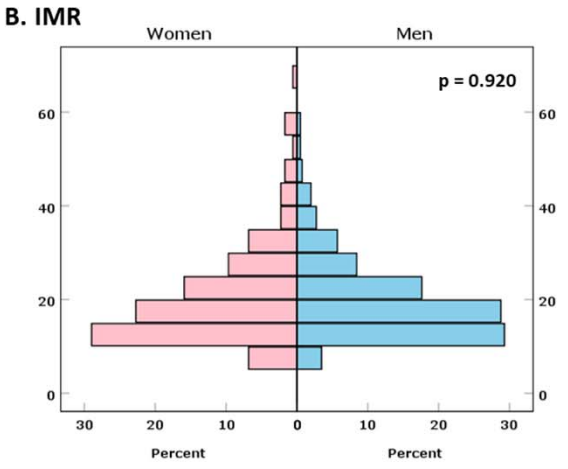
- **Angiographic and physiologic indexes**

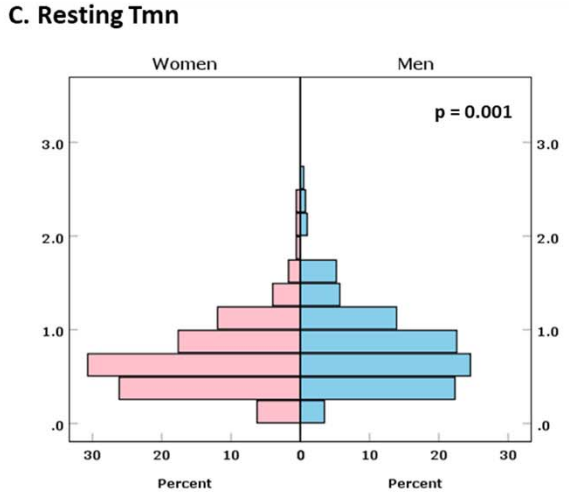
	Total	Women	Men	p value
Per-vessel analysis	n = 579	n = 176	n = 403	
Measured vessel location				0.006
Left anterior descending artery	304 (52.5)	110 (62.5)	194 (48.1)	
Left circumflex artery	120 (20.7)	29 (16.5)	91 (22.6)	
Right coronary artery	155 (26.8)	37 (21.0)	118 (29.3)	
Quantitative coronary angiography				
Reference diameter, mm	3.04 ± 0.60	2.96 ± 0.59	3.07 ± 0.60	0.033
Diameter stenosis, %	37.7 ± 15.1	35.3 ± 14.0	38.7 ± 15.4	0.015
Lesion length, mm	10.2 ± 6.8	9.8 ± 6.7	10.4 ± 6.8	0.356
Coronary physiological parameters				
FFR	0.90 [0.86–0.95]	0.91 [0.87–0.96]	0.90 [0.86–0.95]	0.037
CFR	3.00 [2.20-4.22]	2.69 [2.08-3.90]	3.20 [2.20-4.31]	0.006
IMR	17.2 [13.4-23.4]	17.9 [13.0-25.0]	17.1 [13.7-23.0]	0.920
Resting Tmn	0.72 [0.48-0.99]	0.61 [0.43-0.89]	0.75 [0.49-1.03]	0.001
Hyperemic Tmn	0.22 [0.17-0.30]	0.20 [0.16-0.30]	0.22 [0.17-0.30]	0.058
Vessel-specific CMD*	241 (41.6)	82 (46.6)	159 (39.5)	0.109
CFR ≤2.0	125 (21.6)	43 (24.4)	82 (20.3)	
IMR ≥23	155 (26.8)	53 (30.1)	102 (25.3)	

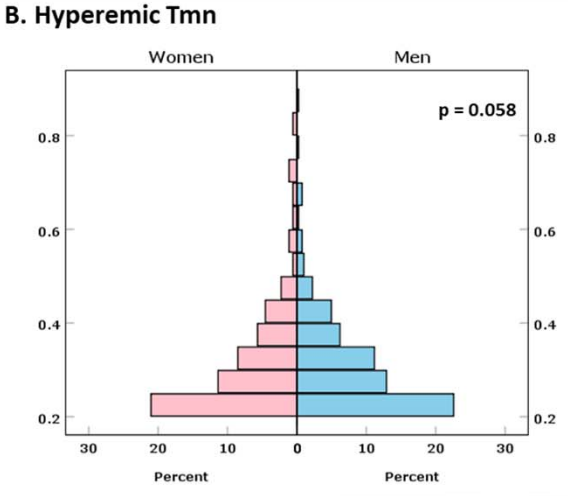
Results

- **Distribution of CFR and IMR according to sex**









Results

- **Clinical outcomes at 5 years**

	Incidence			Unadjusted		Adjusted†	
	Women (n = 176)	Men (n = 403)	p value	HR (95%CI)	p value	HR (95%CI)	p value
Cardiac death	1 (0.6)	13 (3.2)	0.056	5.761 (0.754-44.038)	0.092	7.021 (0.820-60.091)	0.075
Vessel specific myocardial infarction	0	2 (0.5)	0.349	-	-	-	-
Vessel specific revascularization	1 (0.6)	9 (2.2)	0.179	4.060 (0.514-32.047)	0.184	1.981 (0.215-18.279)	0.547
MACE	2 (1.1)	22 (5.5)	0.017	4.911 (1.155-20.885)	0.031	5.164 (1.120-23.804)	0.035

†The included covariables were age, sex, hypertension, diabetes mellitus, hypercholesterolemia, acute coronary syndrome, family history of CAD, current smoking, previous PCI, multivessel disease, ejection fraction, and low CFR.

Results

- **Independent predictors of MACE at 5 years**

	Total		Men*	
	HR (95% CI)	p value	HR (95% CI)	p value
Sex (Men)	5.164 (1.120-23.80)	0.035	-	-
Diabetes mellitus	2.951 (1.209-7.207)	0.017	2.931 (1.125-7.642)	0.028
Low CFR (≤2.0)	4.041 (1.729-9.448)	0.001	4.576 (1.850-11.32)	0.001

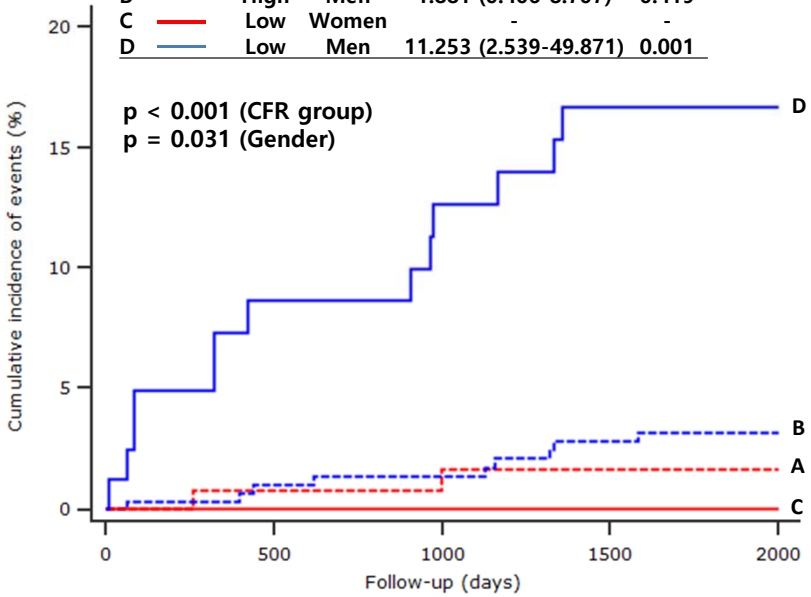
*In the women group, coefficients did not converge due to the small event rates and thus, no model was fitted for further analysis.

Results

- **Cumulative incidence according to CFR and sex**

A. Unadjusted

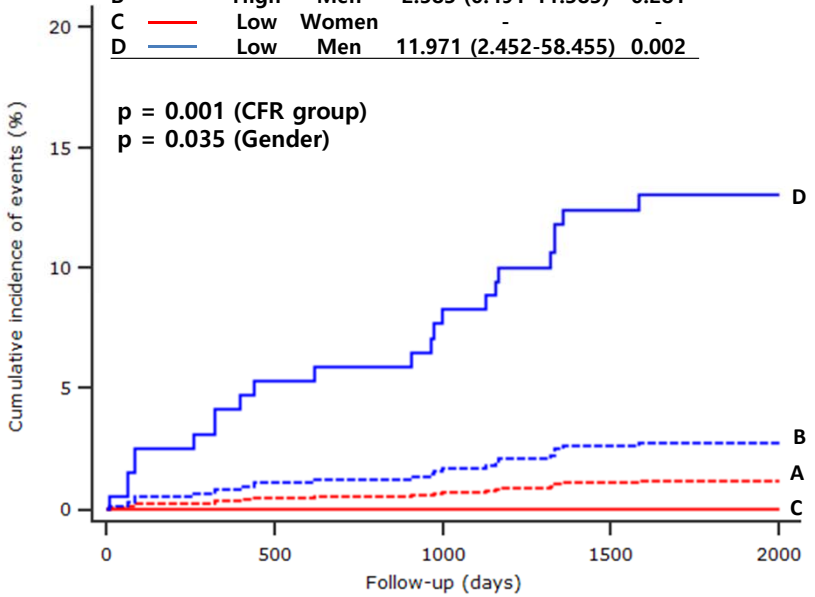
Group	CFR	Sex	Hazard Ratio (95%CI)	p value
A	High	Women	1.000 (Reference)	-
B	High	Men	1.881 (0.406-8.707)	0.419
C	Low	Women	-	-
D	Low	Men	11.253 (2.539-49.871)	0.001



No. at Risk					
A	133	117	116	116	116
B	321	281	278	272	271
C	43	39	38	38	38
D	82	68	65	62	62

B. Adjusted

Group	CFR	Sex	Hazard Ratio (95%CI)	p value
A	High	Women	1.000 (Reference)	-
B	High	Men	2.385 (0.491-11.585)	0.281
C	Low	Women	-	-
D	Low	Men	11.971 (2.452-58.455)	0.002



No. at Risk					
A	133	117	116	116	116
B	321	281	278	272	271
C	43	39	38	38	38
D	82	68	65	62	62

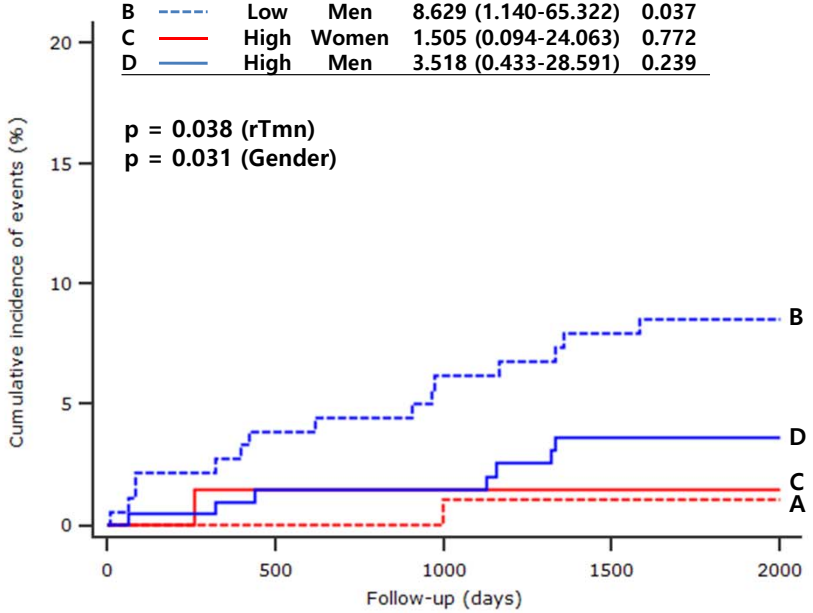
Results

- **Cumulative incidence according to resting mean transit time and sex**

A. Unadjusted

Group	rTmn	Sex	Hazard Ratio (95%CI)	p value
A	Low	Women	1.000 (Reference)	-
B	Low	Men	8.629 (1.140-65.322)	0.037
C	High	Women	1.505 (0.094-24.063)	0.772
D	High	Men	3.518 (0.433-28.591)	0.239

p = 0.038 (rTmn)
p = 0.031 (Gender)

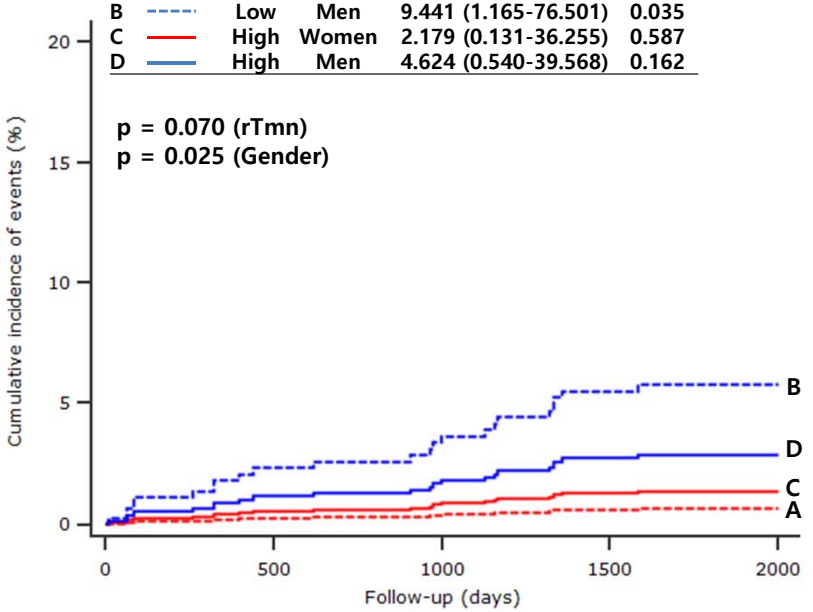


No. at Risk					
A	106	94	92	92	92
B	183	166	161	158	157
C	70	62	62	62	62
D	220	183	182	176	176

B. Adjusted

Group	rTmn	Sex	Hazard Ratio (95%CI)	p value
A	Low	Women	1.000 (Reference)	-
B	Low	Men	9.441 (1.165-76.501)	0.035
C	High	Women	2.179 (0.131-36.255)	0.587
D	High	Men	4.624 (0.540-39.568)	0.162

p = 0.070 (rTmn)
p = 0.025 (Gender)

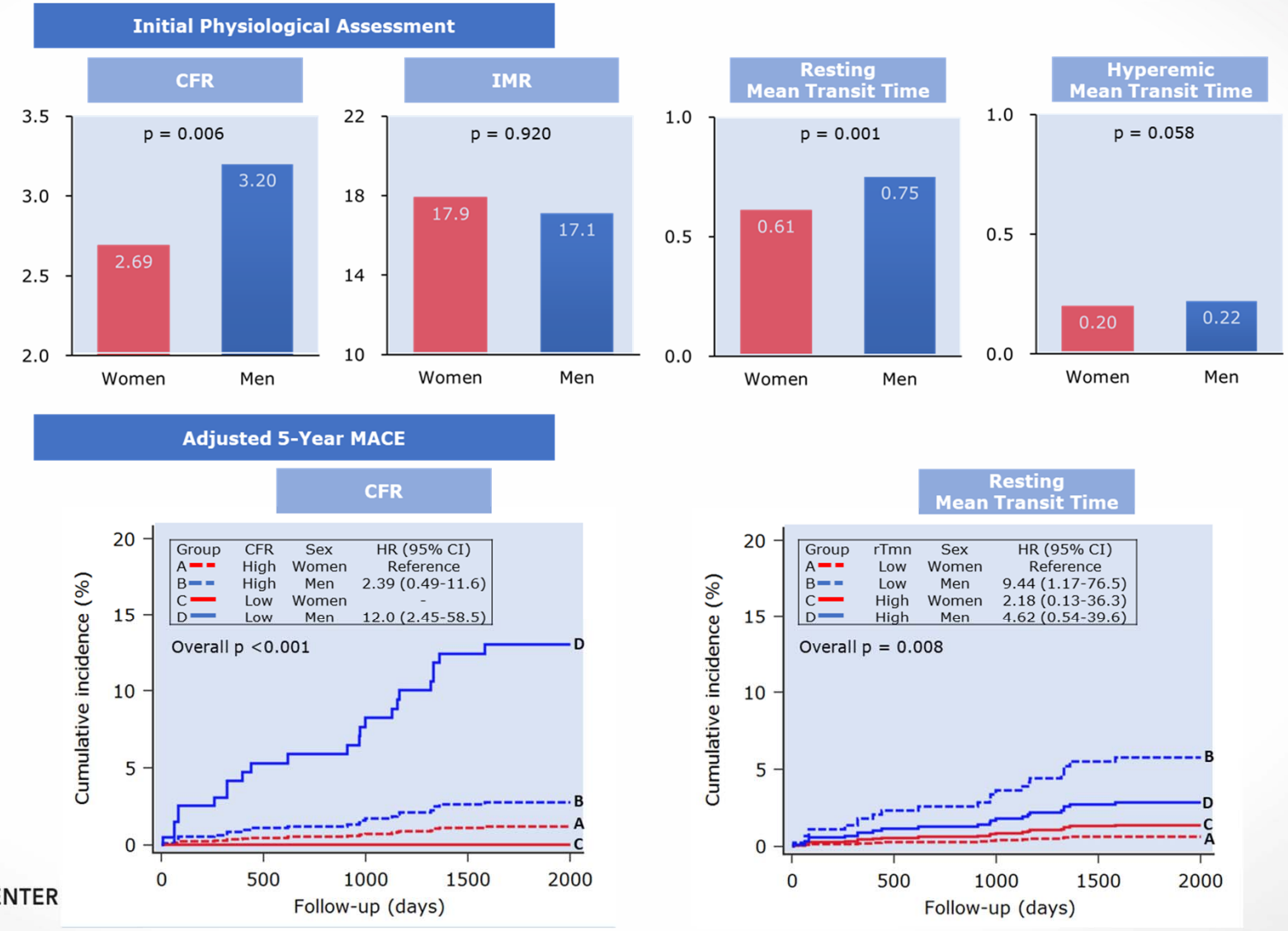


No. at Risk					
A	106	94	92	92	92
B	183	166	161	158	157
C	70	62	62	62	62
D	220	183	182	176	176

Summary

- The prevalence of CMD was high and no different between the sexes
- Resting flow was higher in women while hyperemic flow was similar between the sexes
- Men, diabetes mellitus and low CFR were independent predictors for MACE
- In men, a low versus high CFR resulted in a significant 4.6-fold higher risk of MACE, which was not seen in women.

Summary


Initial Physiological Assessment
CFR
p = 0.006
3.5
3.0
2.5
2.0
2.69
3.20
Women
Men
IMR
p = 0.920
22
18
14
10
17.9
17.1
Women
Men
Resting Mean Transit Time
p = 0.001
1.0
0.5
0.0
0.61
0.75
Women
Men
Hyperemic Mean Transit Time
p = 0.058
1.0
0.5
0.0
0.20
0.22
Women
Men
Adjusted 5-Year MACE
CFR
Group CFR Sex HR (95% CI)
A High Women Reference
B High Men 2.39 (0.49-11.6)
C Low Women -
D Low Men 12.0 (2.45-58.5)
Overall p <0.001
Cumulative incidence (%)
20
15
10
5
0
0
500
1000
1500
2000
Follow-up (days)
D
B
A
C
Resting Mean Transit Time
Group rTmn Sex HR (95% CI)
A Low Women Reference
B Low Men 9.44 (1.17-76.5)
C High Women 2.18 (0.13-36.3)
D High Men 4.62 (0.54-39.6)
Overall p = 0.008
Cumulative incidence (%)
20
15
10
5
0
0
500
1000
1500
2000
Follow-up (days)
B
D
C
A

Conclusion

For deferred lesions

- **There was no difference in microvascular function between men and women by IMR.**
- **CFR was lower in women due to a higher resting coronary flow, however, long-term clinical outcomes in deferred lesions were better in women compared with men.**

Thank you.

Ju-Hyun Chung
Ulsan Medical Center
Dec 13, 2019