



Age at menopause and severity of coronary artery disease among women with Acute Coronary Syndromes

**The LADIES ACS study
(NCT 01997307)**

**Stefano Savonitto
Ospedale A. Manzoni, Lecco - Italy**



Potential conflicts of interest

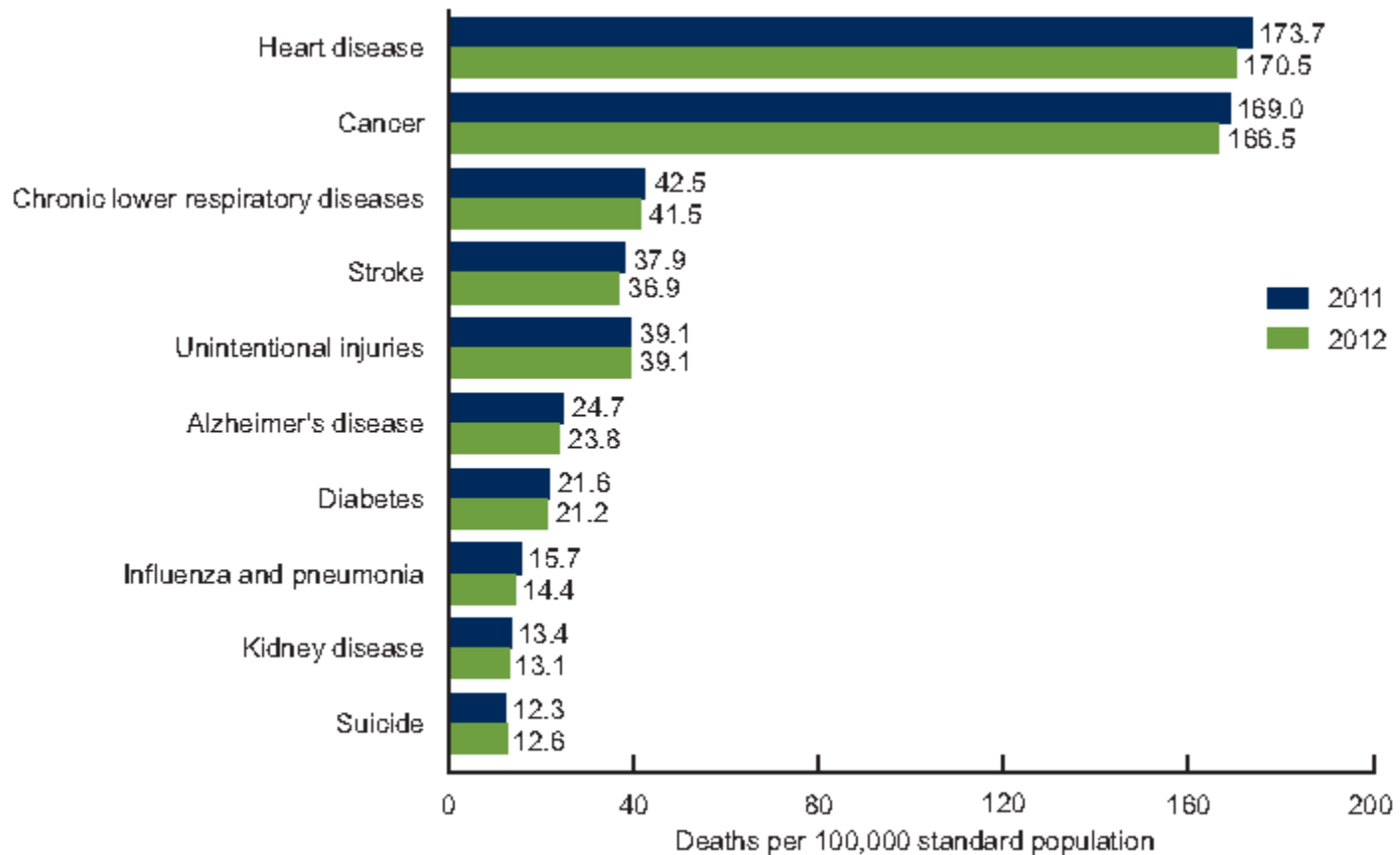


Speaker's name: Stefano Savonitto

I do not have any potential conflict of interest

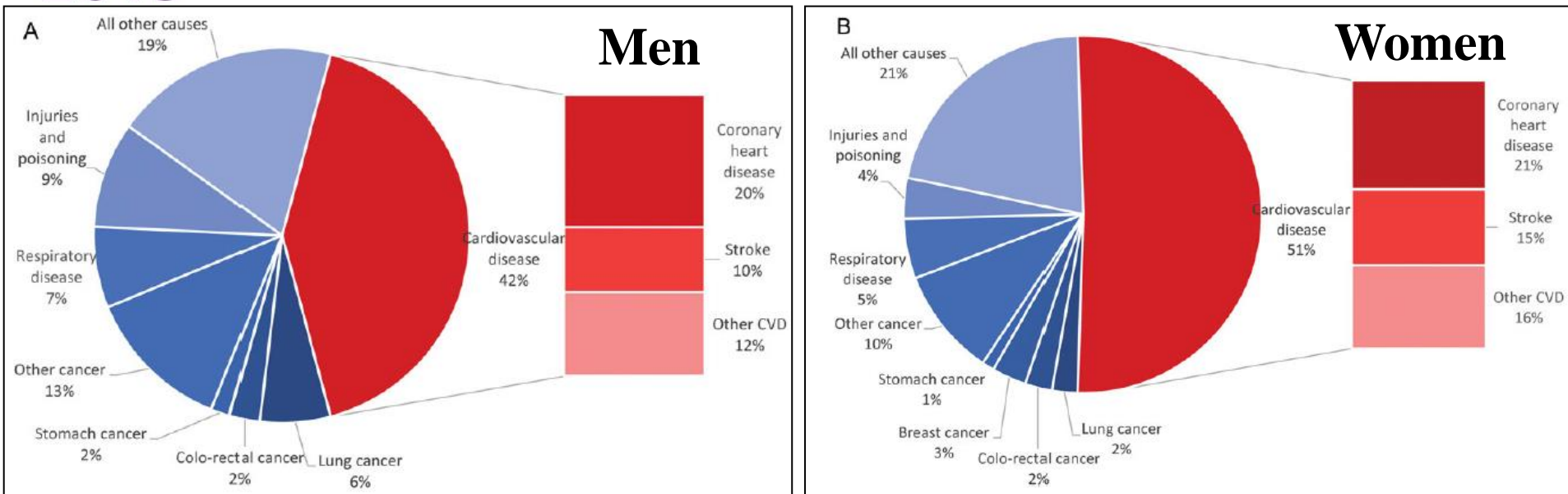


Age-adjusted death rates: 10 leading causes USA 2012



Causes of death in Europe

Source: WHO Mortality Database



Cardiovascular disease (total)

Coronary heart disease

Cerebrovascular disease

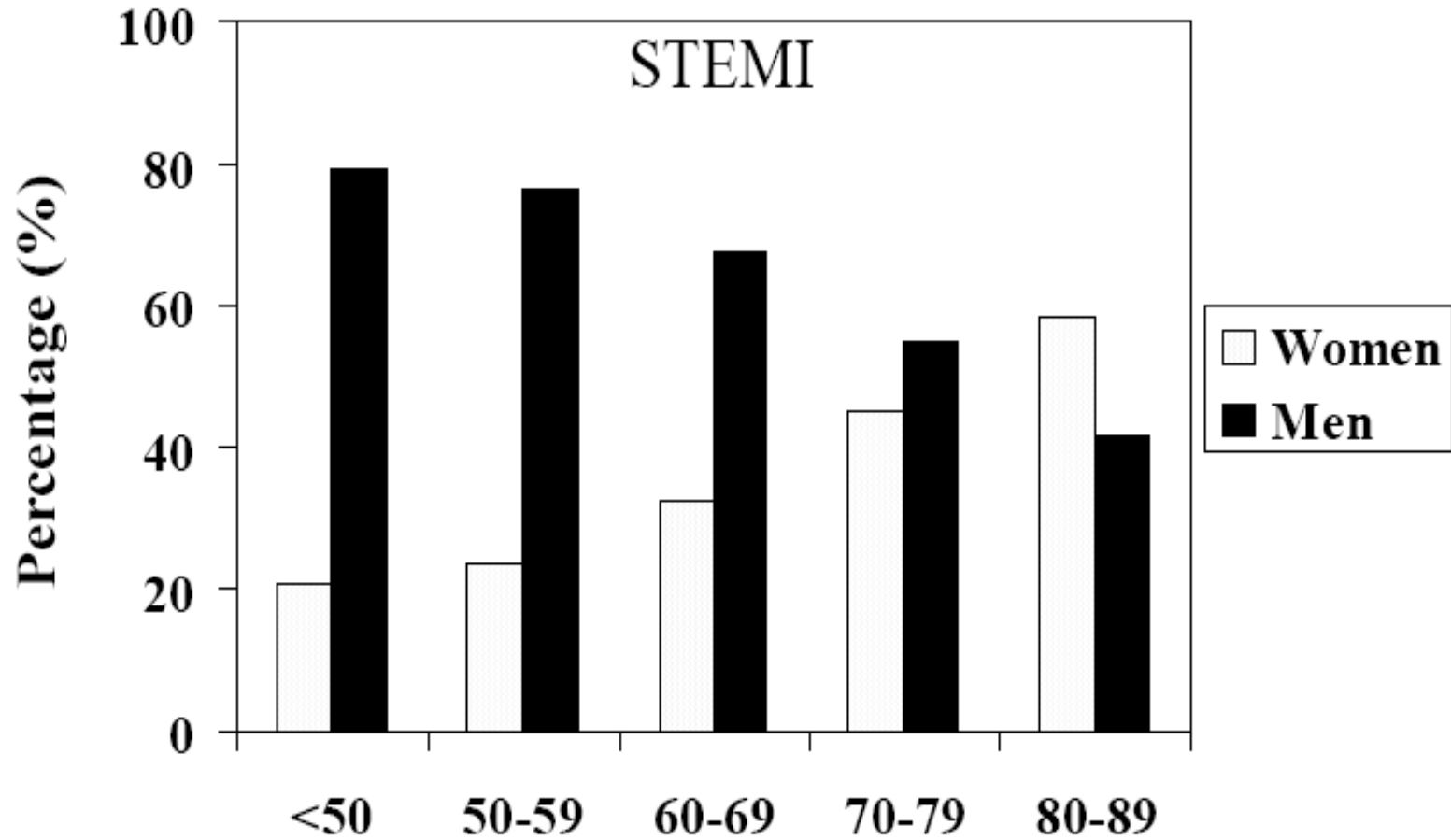
Other cardiovascular diseases



	Cardiovascular disease (total)	Coronary heart disease	Cerebrovascular disease	Other cardiovascular diseases
Males				
Total deaths (all ages)	1 862 774 42%	876 017 20%	429 756 10%	557 001 12%
Premature deaths—before age 75	939 698 36%	473 501 18%	201 780 8%	264 417 10%
Premature deaths—before age 65	508 132 31%	253 432 16%	95 249 6%	159 451 10%
Females				
Total deaths (all ages)	2 219 326 51%	903 330 21%	627 227 14%	688 769 16%
Premature deaths—before age 75	536 712 37%	232 683 16%	155 702 11%	148 327 10%
Premature deaths—before age 65	201 492 27%	77 166 10%	54 470 7%	69 856 9%

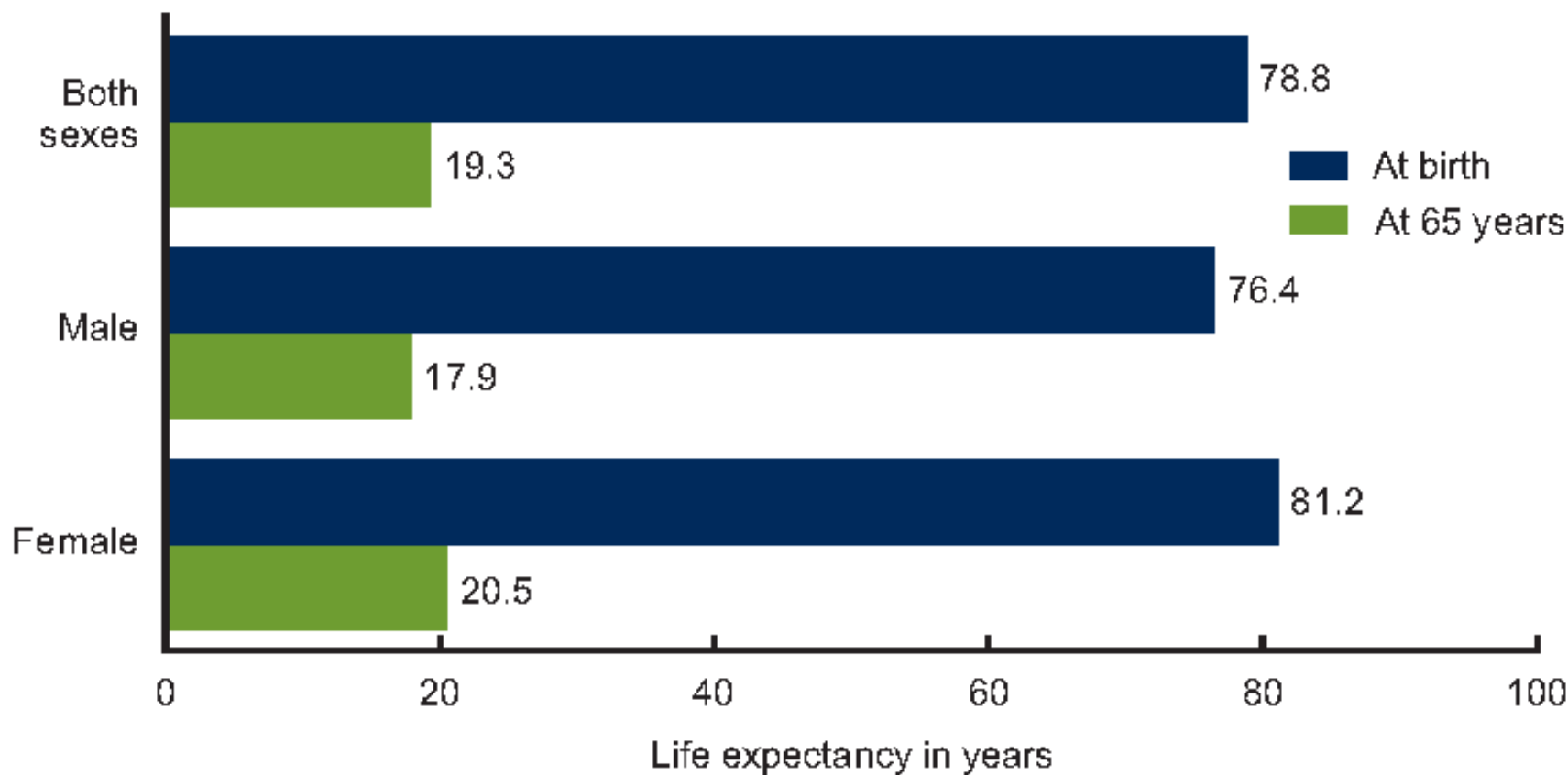


Distribution of STEMI according to age and sex





Life expectancy in the USA 2012



Age at menopause as a risk factor for cardiovascular mortality



**12,115 post menopausal women followed for up to 20 years in a breast cancer program.
824 died for cardiovascular causes**

	Hazard ratio (95% CI)
Crude, adjusted only for biological age	0.982 (0.968–0.996)
Adjusted for all variables simultaneously	0.983 (0.975–0.998)
Adjusted for single variables	
Year of birth	0.982 (0.968–0.996)
Natural menopause	0.981 (0.966–0.996)
Oral contraceptive use	0.983 (0.969–0.998)
Parity/age at first delivery	0.983 (0.969–0.998)
Body-mass index ≥ 30 kg/m ²	0.982 (0.968–0.997)
Upper-body fat distribution	0.982 (0.969–0.996)
Smoking	0.985 (0.971–0.999)
Hypertension	0.982 (0.968–0.996)
Diabetes	0.982 (0.968–0.996)
Previous cardiovascular disease	0.984 (0.969–0.998)

**CV mortality
decreases by 2%
for each year
of delay
in the menopause.**



Female sex hormones



Macrovascular changes



- **Smaller and less compliant arteries**
- **Plaque erosion**
- **Less critical stenoses of coronary arteries**

Microvascular changes



- **Endothelial dysfunction**
- **Smooth muscle cell spasm**

Haemostasis changes



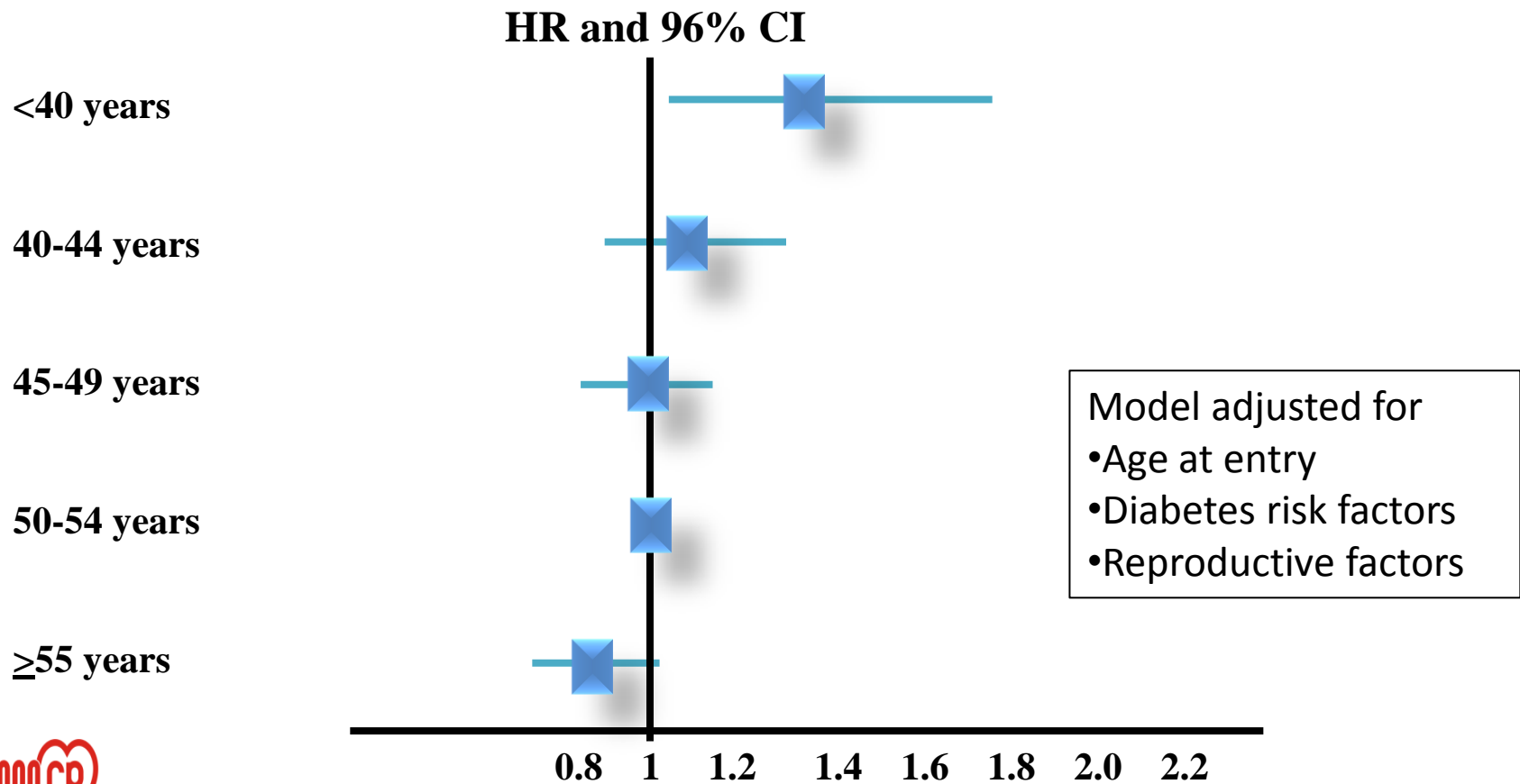
- **Increased platelet reactivity**
- **Hypercoagulable states**

Age at menopause and subsequent risk of type 2 diabetes mellitus

The InterAct study



3,691 postmenopausal type 2 diabetic case subjects and 4,408 subcohort Members
median follow-up of 11 years

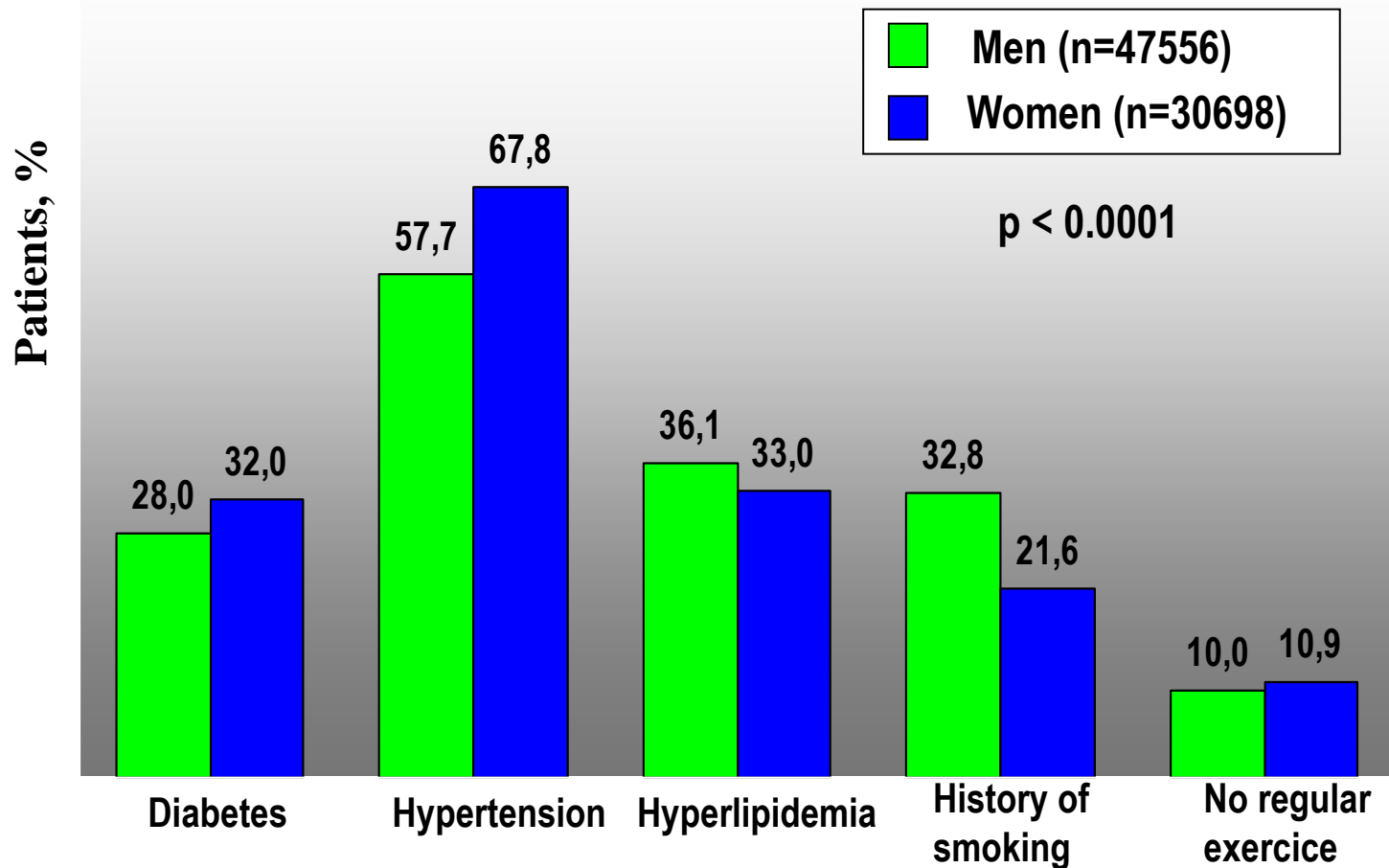


Sex differences in myocardial infarction

Cardiovascular risk factors

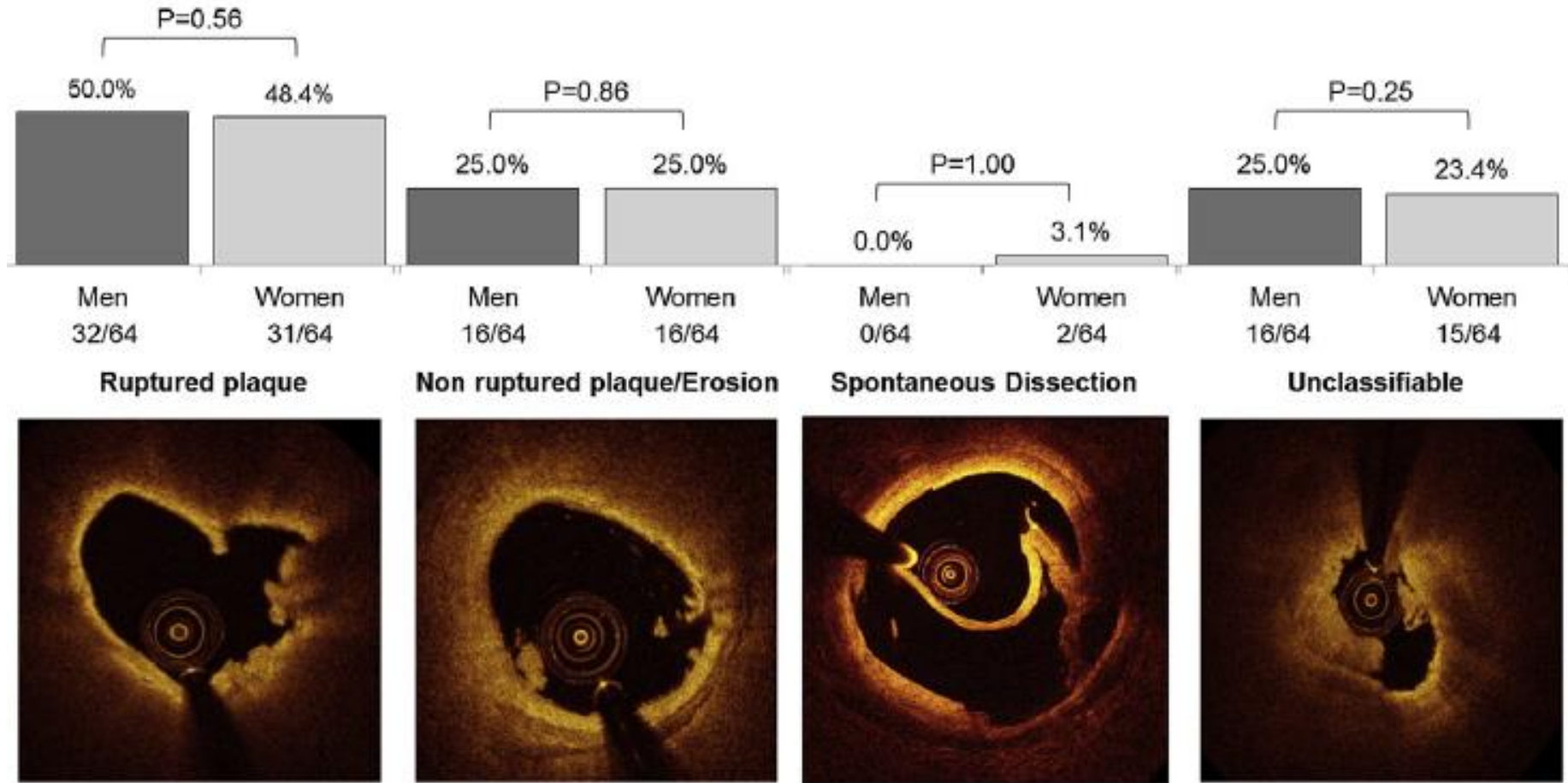


Get With the Guidelines-Coronary Artery Disease Registry



Similar mechanisms of STEMI in women and age-matched men

The OCTAVIA study





To investigate the relation between age at menopause and severity of coronary artery disease in menopausal women with acute coronary syndromes (ACS).



- *Stefano Savonitto*, Ospedale A. Manzoni, Lecco (Principal Investigator)
- *Francesco Prati*, Ospedale San Giovanni, and Rome Heart Research, Rome, (Imaging Corelab)
- *Emilia Lo Jacono, Chiara Leuzzi*, IRCCS Arcispedale S. Maria Nuova, Reggio Emilia (Coordinating Center)
- *Angelo Cagnacci*, Azienda Ospedaliero-Universitaria of Modena (Consultant Gynecologist)
- *Laura Lenatti, Luigi Piatti*, Ospedale A. Manzoni, Lecco
- *Ugo Limbruno, Andrea Picchi*, Ospedale Misericordia di Grosseto
- *Nuccia Morici*, Ospedale Niguarda Ca' Granda, Milano
- *Anna Sonia Petronio*, Cardiothoracic Dept, University of Pisa
- *Giancarlo Piovaccari, Nicoletta Franco*, Ospedale degli Infermi, Rimini
- *Patrizia Presbitero, Elena Corrada*, Humanitas Clinical and Research Center, Rozzano
- *Luigi Tavazzi, Chiara Grattoni* GVM Care&Research, Maria Cecilia Hospital, Cotignola
- *Maria Rosa Conte, Tiziana Aranzulla*, Ospedale Mauriziano, Torino

Sponsor: IRCCS Arcispedale S. Maria Nuova, Reggio Emilia

With unrestricted research grant by Novartis Farma S.p.A., Origgio (*Delia Colombo, Gilberto Bellia*)



Multicenter prospective study in consecutive patients hospitalized with a wide spectrum of ACS and clinical indication to coronary angiography



- Eligible are women and men with a 2:1 enrolment ratio. The men cohort serves as control for concurrent risk factors (age, diabetes, prior history...)
- Patients will be stratified according to gender and age, including four age classes: 55–64, 65–74, 75–84 and ≥ 85 years.

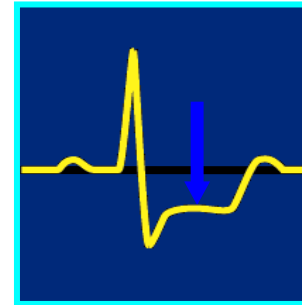
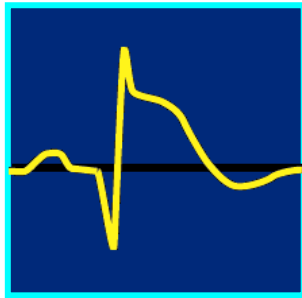
67 men	67 men	67 men	67 men
133 women	133 women	133 women	133 women
55	65	75	85
			≥ 85 years

- Age and gender enrolment will be automatically balanced by Center by the eCRF system

DEFINITION OF ACUTE CORONARY SYNDROME (ACS)



- **Due to the relatively high frequency of aspecific ECG changes among women, eligible for the present study will be patients with both typical ECG changes and typical evolution of serum troponin levels.**



- **Both STEMI and NSTEMI patients are eligible and irrespective of angiographic findings and need for PCI or CABG**



In women fertility history will be captured by specific items, including:

- **age at first and last menstrual period,**
- **past use of oral contraceptives,**
- **ongoing and past hormone replacement therapy (HRT)**
- **hysterectomy and/or oophorectomy,**
- **number of full-term pregnancies (the sum of live births and stillbirths).**

Reproductive life span is automatically calculated by subtracting the age at menarche from the age at menopause.

The presence of hot flushes, their severity and duration in years will be also captured.



- **The primary angiographic endpoint will be the severity of CAD, as appraised by the Gensini score, which includes both angiographically non-significant and significant stenoses**
- **Specifically, according to the Gensini score, the narrowing of the coronary lumen is graded as follows:**

1 point, $\leq 25\%$
2 points, 26-50%
4 points, 51-75%
8 points, 76-90%
16 points, 91-9%
32 points, 100%

This primary score is multiplied by a factor that takes into account the importance of the coronary artery containing the Lesion:

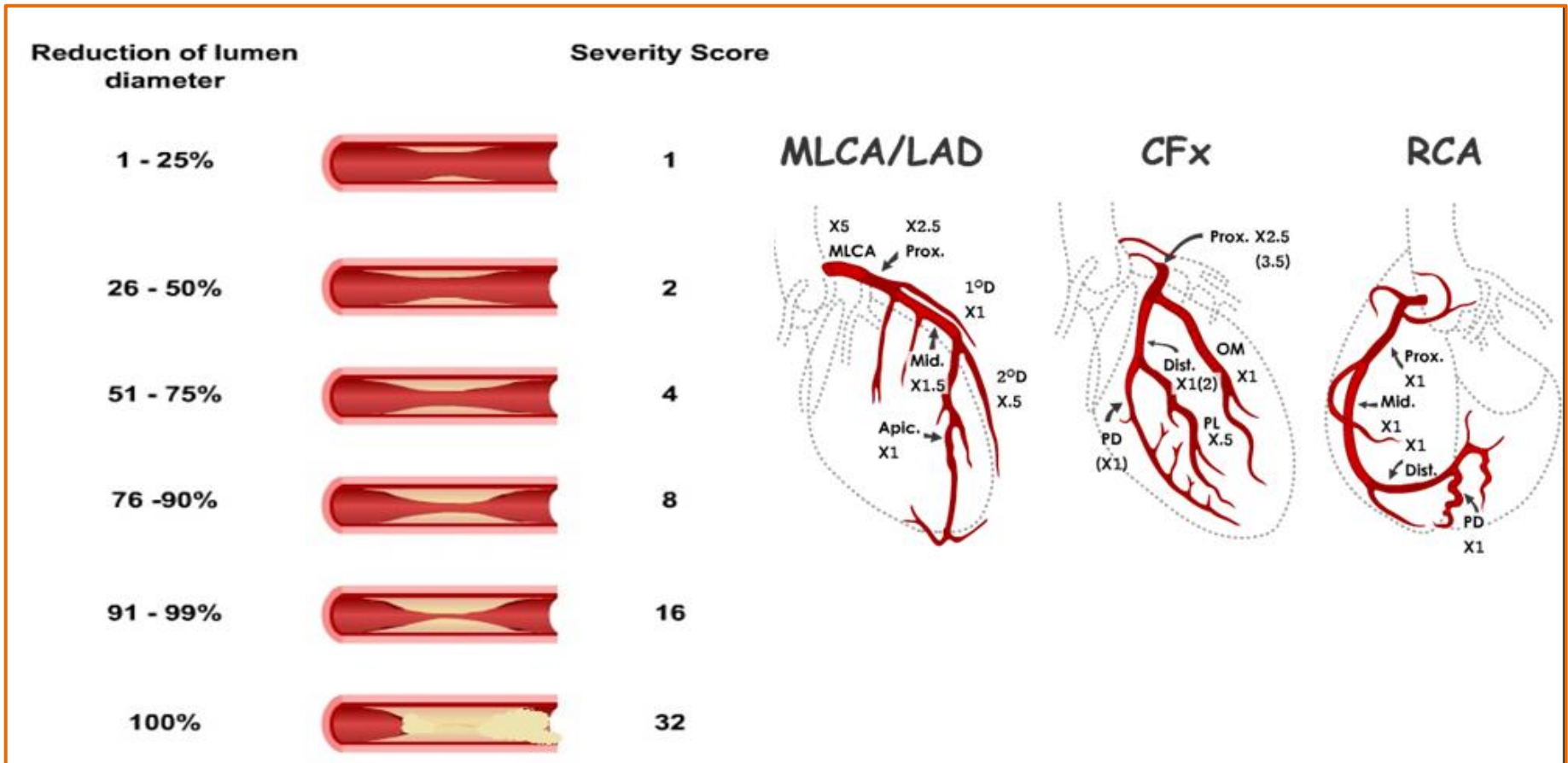
- **5 for the left main coronary artery,**
- **2.5 for the proximal portion of the left anterior descending artery or proximal left circumflex artery and**
- **1.5 for the midregion,**
- **1 for the distal left anterior descending artery, and**
- **1 for the mid-distal region of the left circumflex artery or right coronary artery.**

The sum of the total score obtained will be used for statistical analysis.

GENSINI SCORE



The score computes the severity of coronary narrowing (including “noncritical” stenoses) in each coronary segment multiplied by the hierarchical importance of the specific segment.





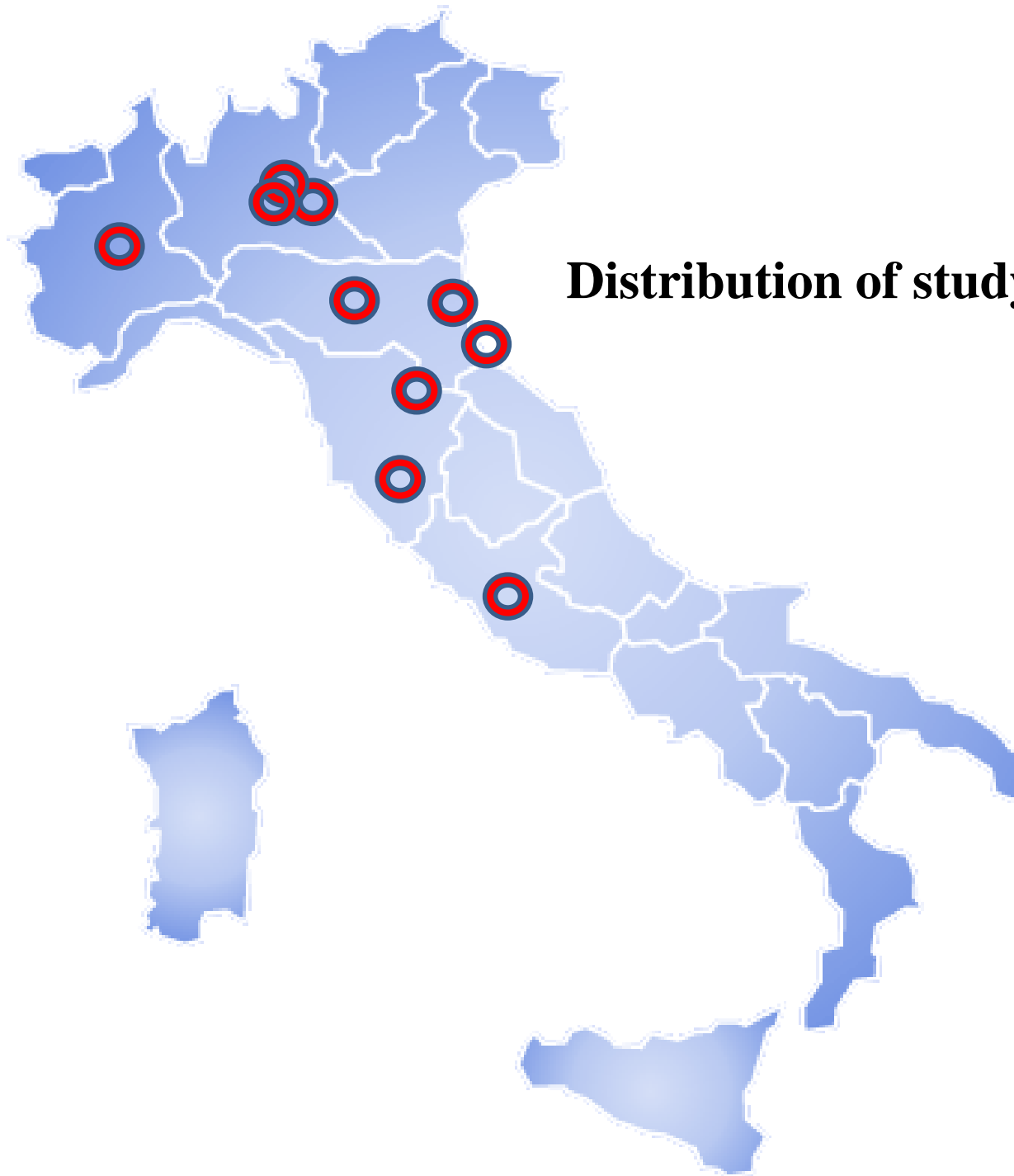
Scoring system	No. of citations in MEDLINE/Google Scholar	No. of vessels involved	Severity of lesion	Functional significance of lesion	Comments
Gensini*	962	+++	+++	+++	Most widely used
CASS*	181	++	++	+	Oldest scoring system
Duke CAD Severity Index*	286	++	+++	++	Prognostic value
Syntax	783	+++	+++	+	Requires computer algorithm
Duke Jeopardy*	317	+++	++	++	Widely used, well validated
BARI Jeopardy Index	100	+++	++	++	Requires computer algorithm
Jenkins*	212	+++	+++	+	Uses proximal disease only
Friesinger*	273	+	+++	+	Modifies CASS score
Sullivan*	149	+++	+++	+++	3 separate scores
Approach	45	+++	++	+++	Varies with coronary anatomy

Interscore correlation coefficients

	Gensini	CASS-50	CASS-70	Duke Jeopardy	Duke CAD Severity Index	Friesinger	Sullivan Vessel	Sullivan Stenosis	Sullivan Extent
CASS-50	0.89*								
CASS-70	0.90*	0.94*							
Duke Jeopardy	0.90*	0.83*	0.89*						
Duke Severity CAD Index	0.93*	0.87*	0.89*	0.92*					
Friesinger	0.92*	0.86*	0.87*	0.83*	0.90*				
Sullivan Vessel	0.88*	0.88*	0.94*	0.89*	0.93*	0.90*			
Sullivan Stenosis	0.94*	0.95*	0.92*	0.86*	0.88*	0.91*	0.87*		
Sullivan Extent	0.90*	0.88*	0.85*	0.77*	0.81*	0.88*	0.79*	0.96*	
Jenkins	0.94*	0.93*	0.91*	0.86*	0.89*	0.92*	0.88*	0.98*	0.94*



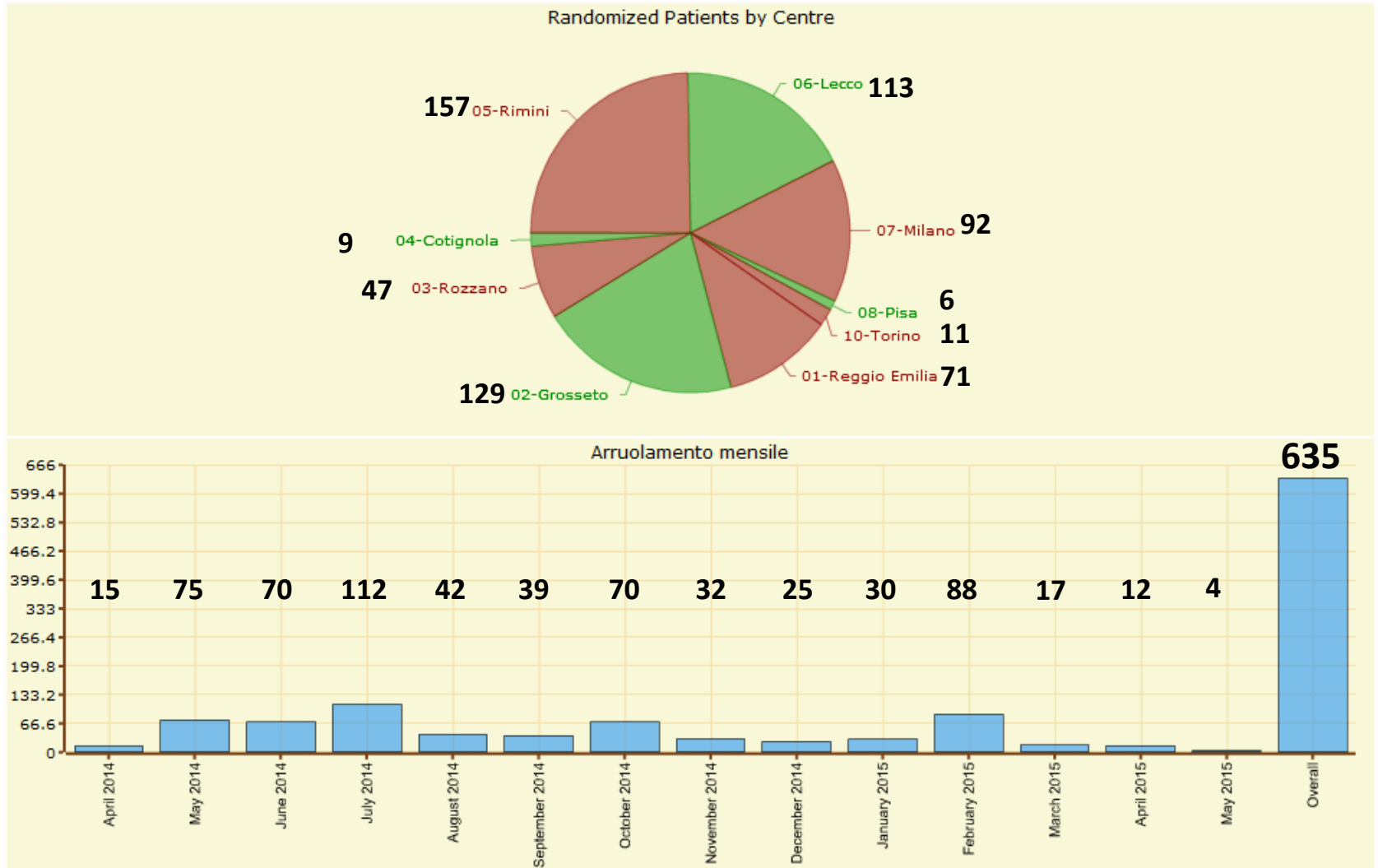
- We assumed an average Gensini score of 16.0 in the overall group of women (with SD 6.0)
- By enrolling a total of 530 women (and 265 men), our study will be able to detect an absolute difference of ≥ 2.0 in Gensini score between 2 groups of women with different baseline features (e.g. age at menopause <50 vs >50 years, or below vs above median of the study population), achieving 97% power and 5% 2-tailed alpha.
- Such a high power for the primary analysis will allow enough power to investigate for how long any observed difference will last after menopause, with age divided into tertiles (power 0.85 with two-sided alpha at 0.05).



Distribution of study Centers

Enrolment status May 8, 2015

By Center and month



Enrolment status May 8, 2015 by age/sex strata (N= 635)

