11° CONGRESSO NAZIONALE

CAMPUS Cuore

Quello che le Linee Guida Non Dicono

Napoli
5-6 aprile 2024

Prof Alaide Chieffo, FESC, FSCAI
Università Vita Salute San Raffaele Presidente Eletto EAPCI
UO Cardiologia Interventistica (2022-2024)
IRCCS Ospedale San Raffaele
Milano

INOCA E MINOCA

ITER DIAGNOSTICO E STRATEGIE TERAPEUTICHE

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Presidente Eletto EAPCI
(2022-2024)

ESC European Society of Cardiology

European Heart Journal (2020) **0**, 1–21
doi:10.1093/eurheartj/ehaa503

SPECIAL ARTICLE
Coronary artery disease

An EAPCI Expert Consensus Document on Ischaemia with Non-Obstructive Coronary Arteries in Collaboration with European Society of Cardiology Working Group on Coronary Pathophysiology & Microcirculation Endorsed by Coronary Vasomotor Disorders International Study Group

Vijay Kunadian (UK, Document Chair)[1*†], Alaide Chieffo (Italy, Document Co-Chair)[2†], Paolo G. Camici(Italy)[3], Colin Berry (UK)[4], Javier Escaned (Spain)[5], Angela H. E. M. Maas (Netherlands)[6], Eva Prescott(Denmark)[7], Nicole Karam (France)[8], Yolande Appelman (Netherlands)[9], Chiara Fraccaro (Italy)[10], Gill Louise Buchanan(UK)[11], Stephane Manzo-Silberman(France)[12], Rasha Al-Lamee (UK)[13], Evelyn Regar (Germany)[14], Alexandra Lansky (USA, UK)[15,16], J. Dawn Abbott (USA)[17], Lina Badimon (Spain)[18], Dirk J. Duncker (Netherlands)[19], Roxana Mehran (USA)[20], Davide Capodanno(Italy)[21], and Andreas Baumbach [22,23](UK, USA)

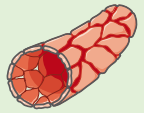
[1]Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University and Cardiothoracic Centre, Freeman Hospital, Newcastle upon Tyne NHS Foundation Trust, M4146 4th Floor William Leech Building, Newcastle upon Tyne NE2 4HH, UK; [2]IRCCS San Raffaele Scientific Institute, Milan, Italy; [3]Vita Salute University and San Raffaele Hospital, Milan, Italy; [4]British Heart Foundation Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK; [5]Hospital Clinico San Carlos IDISSC, Complutense University, Madrid, Spain; [6]Department of Cardiology, Radboud University Medical Center, Nijmegen, the Netherlands; [7]Department of Cardiology, Bispebjerg University Hospital, Copenhagen, Denmark; [8]European Hospital Georges Pompidou (Cardiology Department), Paris University and Paris Cardiovascular Research Center (INSERMU970), Paris, France; [9]Department of Cardiology, Amsterdam UMC, Location VU University Medical Center, Amsterdam, the Netherlands; [10]Department of Cardiac, Thoracic and Vascular Science and Public Health, Padova, Italy; [11]North Cumbria Integrated Care NHS Foundation Trust, Cumbria, UK; [12]Department of Cardiology, Lariboisière Hospital Paris University, Paris, France; [13]National Heart and Lung Institute, Imperial College London, London, UK; [14]Ludwig-Maximilians-University, Munich, Germany; [15]Section of Cardiovascular Medicine, Yale University School of Medicine, New Haven, CT, USA; [16]Bart's Heart Centre, St Bartholomew's Hospital, West Smithfield, London, UK; [17]Lifespan Cardiovascular Institute and Warren Alpert Medical School of Brown University, Providence, RI, USA; [18]Cardiovascular Program-ICCC, IR-Hospital de la Santa Creu i Sant Pau, CiberCV, Barcelona, Spain; [19]Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands; [20]Zena and Michael A. Wiener Cardiovascular Institute, Mount Sinai Hospital, New York, NY, USA; [21]CardioThoracic-Vascular and Transplant Department, A.O.U. 'Policlinico-Vittorio Emanuele', University of Catania, Catania, Italy; [22]Centre for Cardiovascular Medicine and Devices, William Harvey Research Institute, Queen Mary University of London and Barts Heart Centre, London, UK; and [23]Yale University School of Medicine, New Haven, CT, USA

Received 3 February 2020; editorial decision 29 May 2020; accepted 1 June 2020

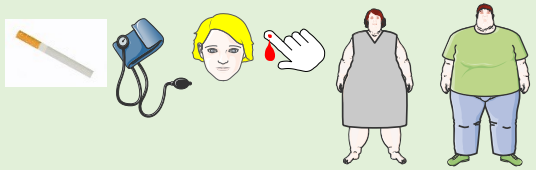
Ischaemia with non obstructive coronary arteries (INOCA)

Coronary Microvascular dysfunction (CMD)

Coronary microcirculation

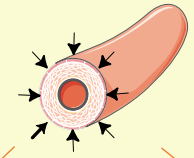


Impairs coronary physiology and myocardial blood flow in subjects with risk factors



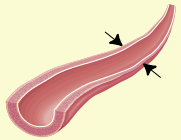
Causes microvascular angina and contributes to myocardial ischaemia in CAD

Vasospastic angina (VSA)



Transient vasospasm

Prinzmetal angina



Persistent vasospasm

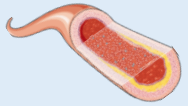
Myocardial infarction

Non-obstructive coronary atherosclerosis is frequently present.

Ischaemia with obstructive coronary artery disease

Atherosclerotic disease

Epicardial coronary artery

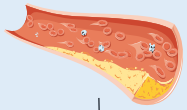


Stable plaque

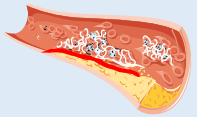
Reduction in FFR

Demand ischaemia ± angina

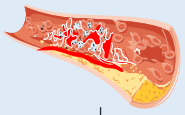
Vulnerable plaque



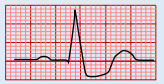
Plaque rupture



Thrombosis



Acute coronary syndromes/infarction



These mechanisms can overlap

European Heart Journal (2020) **41**, 3504–3520
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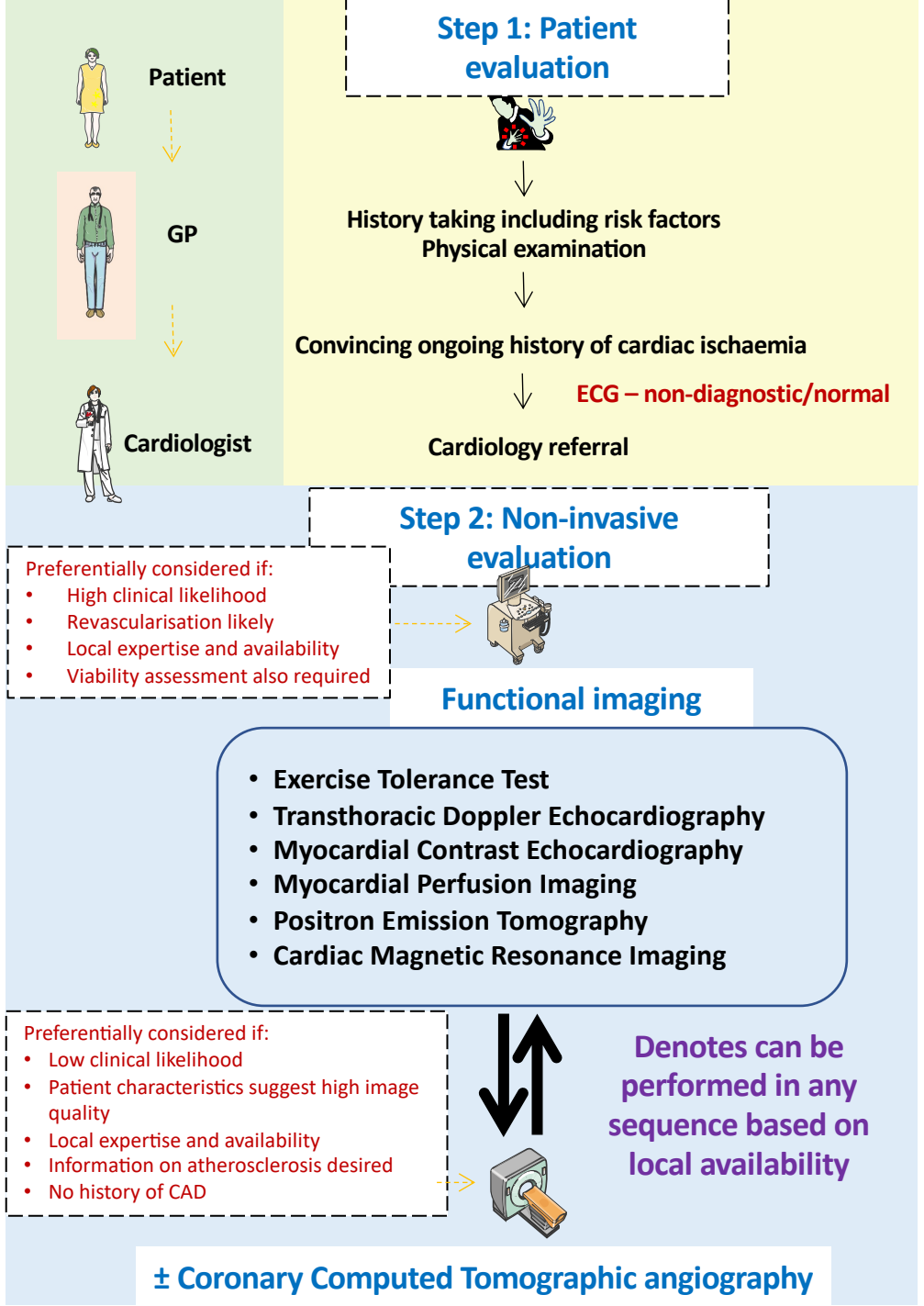
Non Invasive Evaluation



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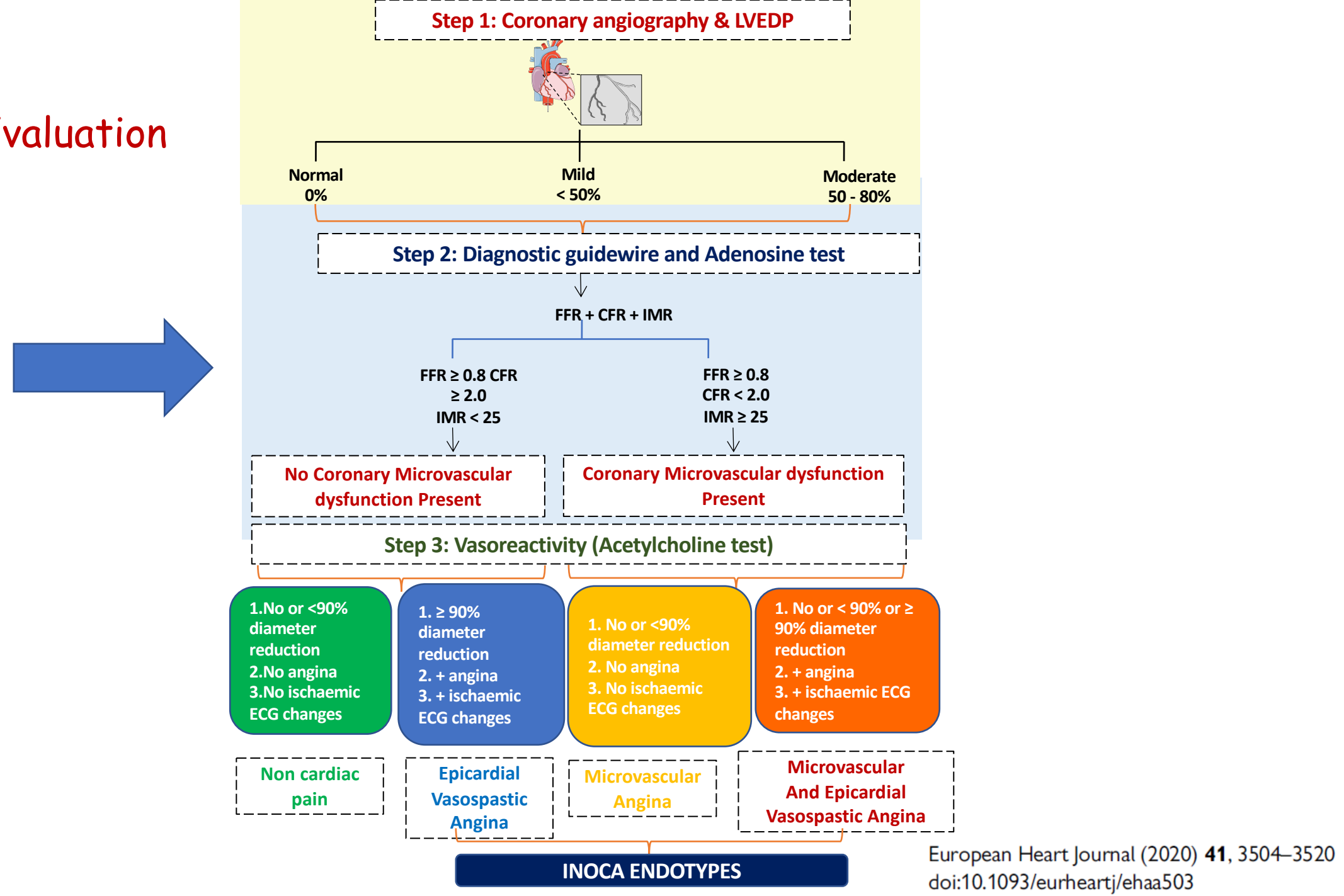

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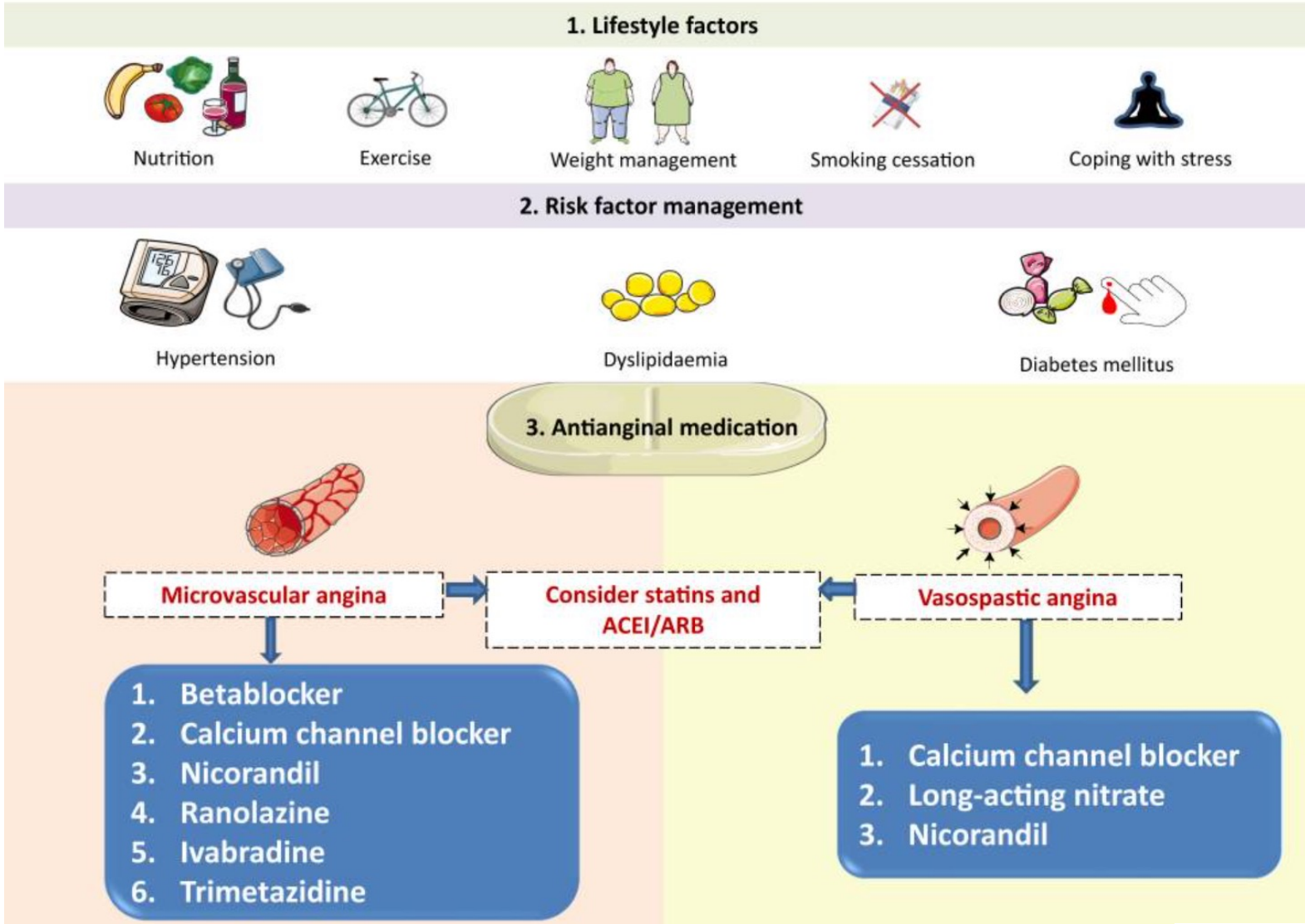
Management of INOCA



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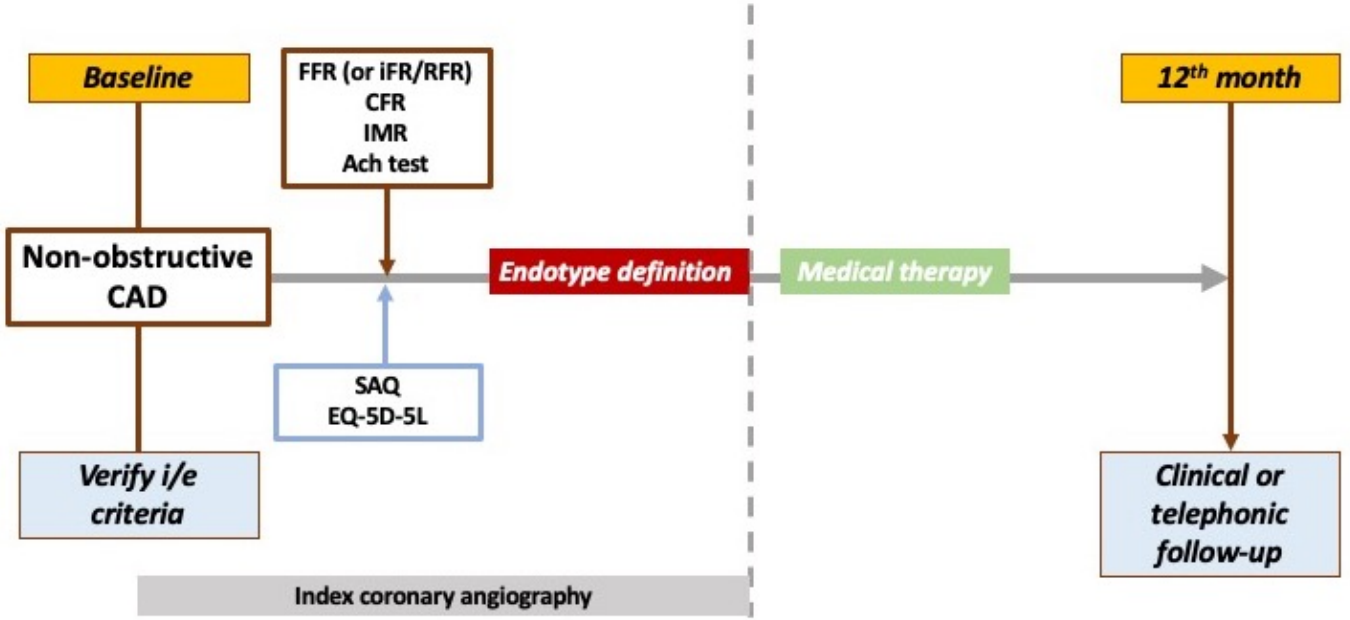
Ischemia in patients with non-obstructive disease (INOCA) in Italy

INOCA IT Multicenter Registry (RF-2019-12369486)

- Multicenter, prospective, non-randomized, single-arm, open label clinical study
- 200 patients with angina and/or positive stress test undergoing clinical indicated CA detecting non obstructive CAD



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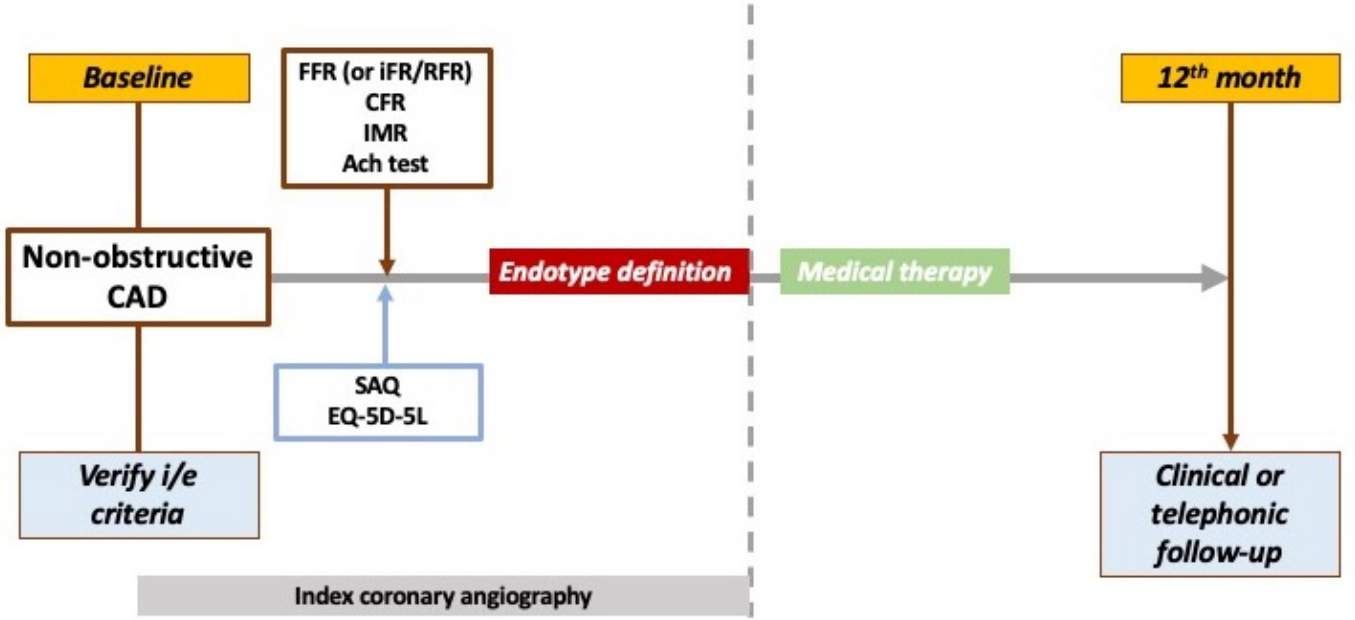

Ghizzoni G.. Chieffo A International Journal of Cardiology 2024 in press

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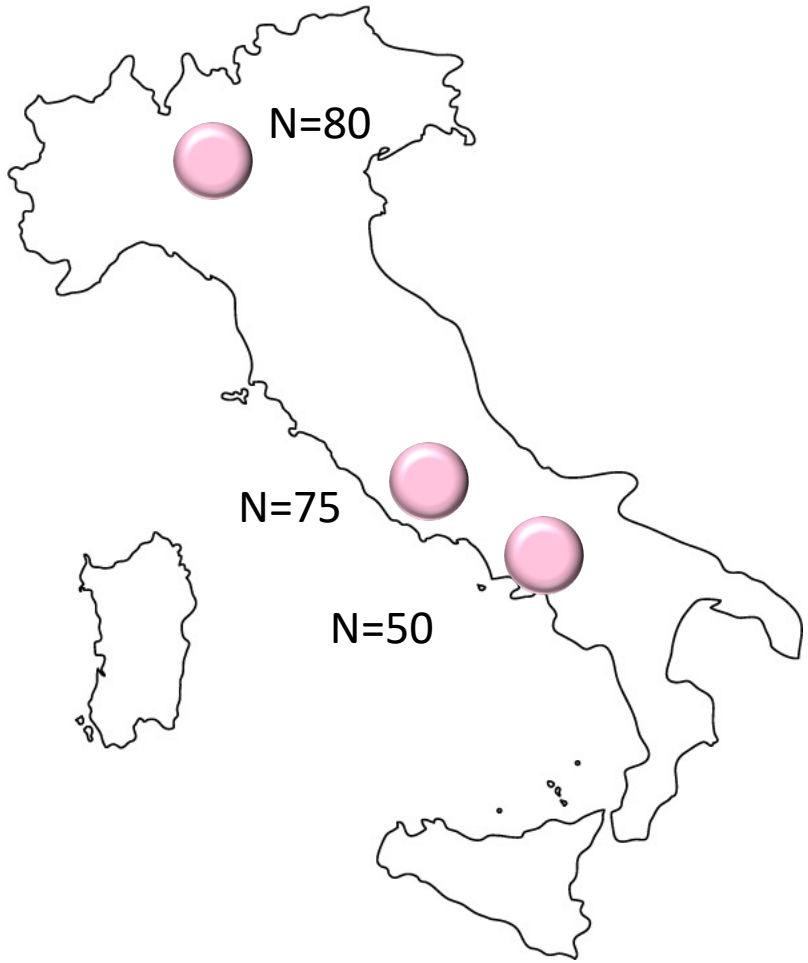
Centers involved

- U.O Emodinamica e Cardiologia interventistica, IRCCS Ospedale San Raffaele, **Milano**
- Dipartimento di Scienze Cardiovascolari e Toraciche Fondazione Policlinico Universitario A. Gemelli IRCCS, **Roma**
- Dipartimento Assistenziale Integrato di Emergenze Cardiovascolari, Medicina Clinica e dell'Invecchiamento Azienda Ospedaliera Universitaria Federico II, **Napoli**



205 pazienti arruolati!!

Arruolamento terminato 29/02/2024

Ischemia in patients with non-obstructive disease (INOCA)
in Italy:
INOCA IT Multicenter Registry. (RF-2019-12369486)

Study Objectives

1. To investigate the prevalence of INOCA in women vs. men who are referred for a clinically indicated coronary angiography in three Centers in Northern, Central and Southern Italy

2. To stratify in INOCA endotypes patients according to the presence or absence of alternative (i.e. non obstructive CAD) causes of myocardial ischemia detected during CA clinically indicated through physiology tests

3. To implement a stratified therapy in these patients considering the different INOCA endotypes and evaluate the impact on angina class and quality of life as well as cardiac hospitalization and coronary revascularization during 1 year follow up

Ischemia in patients with non-obstructive disease (INOCA) in Italy

INOCA IT Multicenter Registry. (RF-2019-12369486)

Enrolment

Acronimo RF-2019-12369486 "Ischemia in patients with non-obstructive disease (INOCA) in Italy INOCA IT Multicenter registry"

FOGLIO INFORMATIVO,
DICHIARAZIONE DI CONSENSO
E INFORMATIVA PRIVACY
per un paziente adulto capace di dare personalmente il consenso

Modulo di consenso informato: Versione 3.0 del 12/07//2021

Parte 1

Gentile signora/e,

1) In questo Istituto Le viene proposto di partecipare ad una ricerca clinica sul ruolo d
parametri di funzionalità (fisiologia) del microcircolo coronarico per l'identificazione e la caratt
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Migliorare la conoscenza della malattia del paziente.
In particolare, con la ricerca che qui Le presentiamo,
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Appendix

The Seattle Angina Questionnaire

1. The following is a list of activities that people often do during the week. Although for some people with several medical problems it is difficult to determine what it is that limits them, please go over the activities listed below and indicate how much limitation you have had **due to chest pain, chest tightness, or angina over the past 4 weeks.**

Place an x in one box on each line.

Activity	Severely Limited	Moderately Limited	Somewhat Limited	A Little Limited	Not Limited	Limited, or did not do for other reasons
Dressing yourself	☐	☐	☐	☐	☐	☐
Walking indoors on level ground	☐	☐	☐	☐	☐	☐
Showering	☐	☐	☐	☐	☐	☐
Climbing a hill or a flight of stairs without stopping	☐	☐	☐	☐	☐	☐
Gardening, vacuuming, or carrying groceries	☐	☐	☐	☐	☐	☐
Walking more than a block at a brisk pace	☐	☐	☐	☐	☐	☐
Running or jogging	☐	☐	☐	☐	☐	☐
Lifting or moving heavy objects (e.g. furniture, children)	☐	☐	☐	☐	☐	☐
Participating in strenuous sports (e.g. swimming, tennis)	☐	☐	☐	☐	☐	☐

2. Compared with 4 weeks ago, how often do you have **chest pain, chest tightness, or angina** when doing your **most strenuous** level of activity?
I have had **chest pain, chest tightness,** or **angina**...

Much more often	Slightly more often	About the same	Slightly less often	Much less often
☐	☐	☐	☐	☐

3. Over the past 4 weeks, on average, how many times have you had **chest pain, ch tightness, or angina?**
I get **chest pain, chest tightness,** or **angina**...

4 or more times per day	1-3 times per day	3 or more times per week but not every day	1-2 times per week	Less than once a week	None over the past 4 weeks
☐	☐	☐	☐	☐	☐

EQ-5D-5L

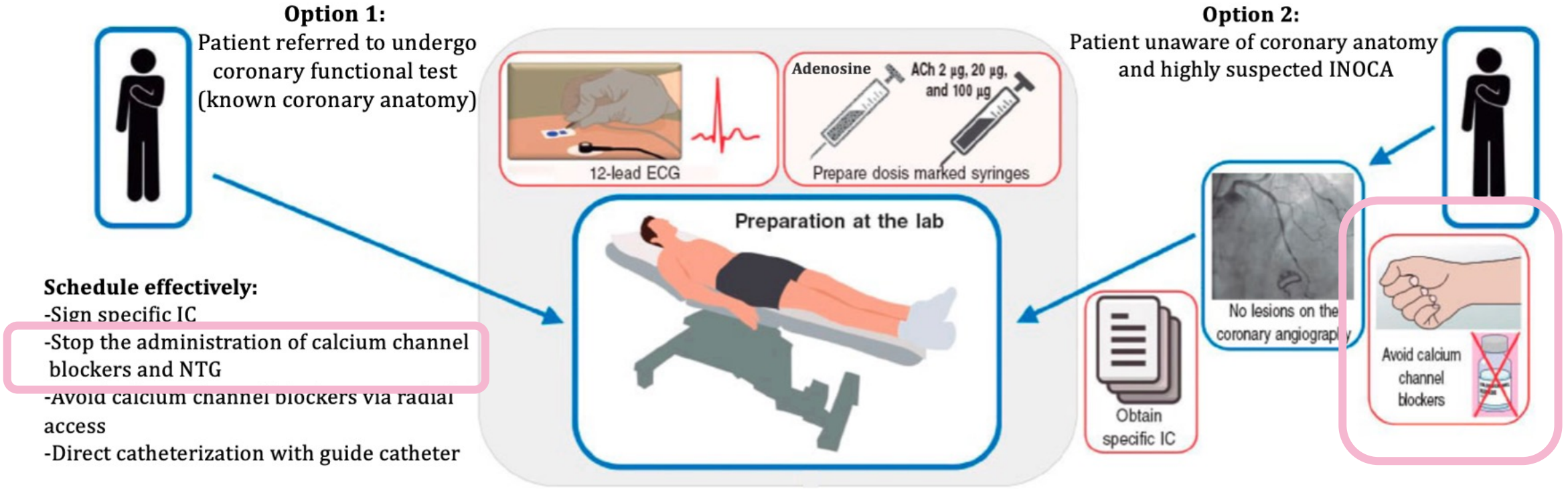
Questionario sulla Salute

Versione italiana per l'Italia

(Italian version for Italy)

In the Cath Lab…

Ischemia in patients with non-obstructive disease (INOCA) in Italy: INOCA IT Multicenter Registry. (RF-2019-12369486)



Readapted from Interv Cardiol. 2021; 3(4):286-296. doi.org/10.24875/RECICE.M21000215

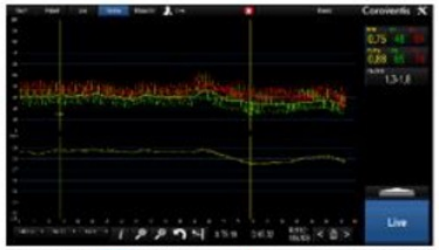
Coronary function testing: Diagnostic guidewire and Adenosine test

- Intravenous Adenosine (140 mcg/kg/min) to inducing steady-state hyperaemia and achieve endothelium-independent vasodilation

Coronary function testing: Diagnostic guidewire and Adenosine test

Epicardial assessment

- FFR, RFR, Pd/Pa
- Pullback

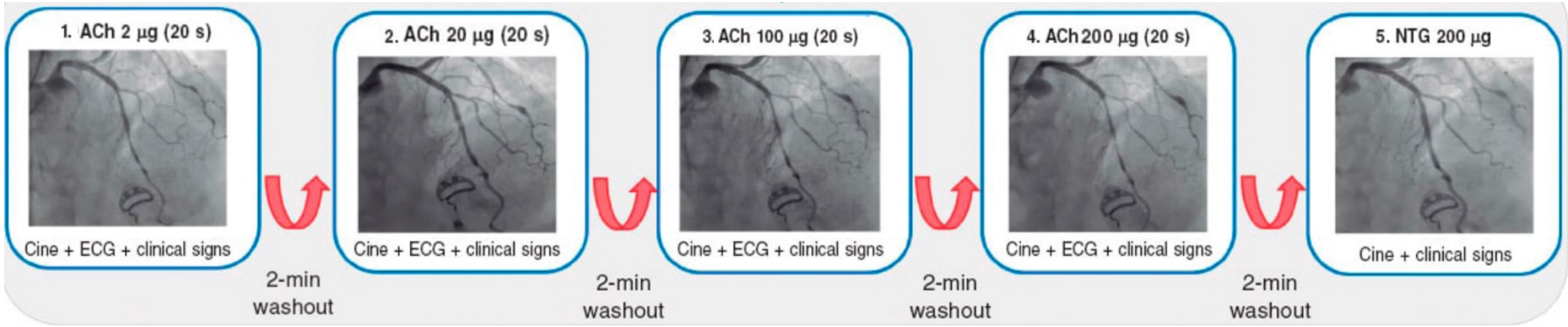


Microvascular assessment

- IMR, RRR
- CFR, PB-CFR
- Absolute Flow/Resistance

From Coroventis.com

Acetylcholine Test



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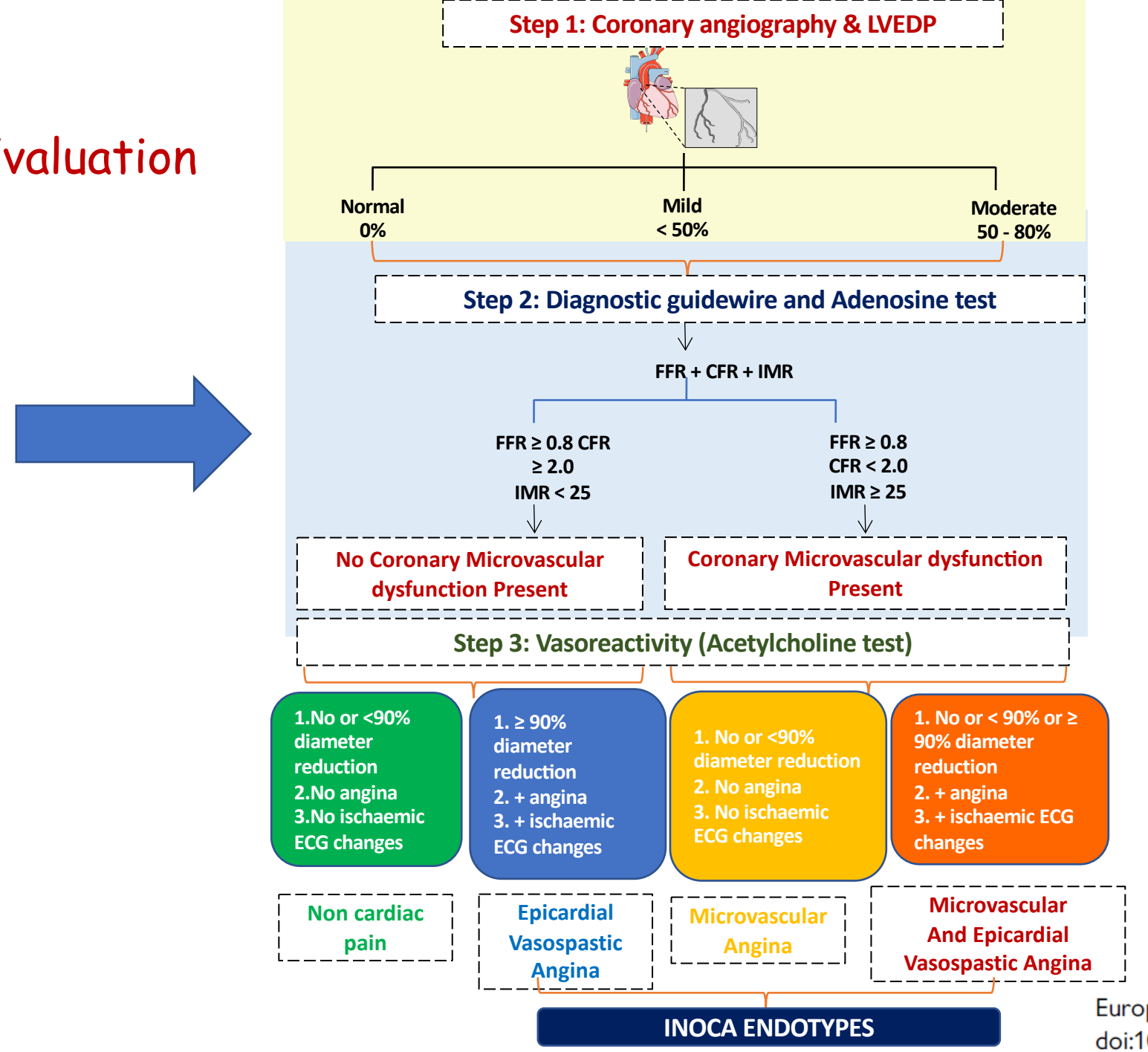

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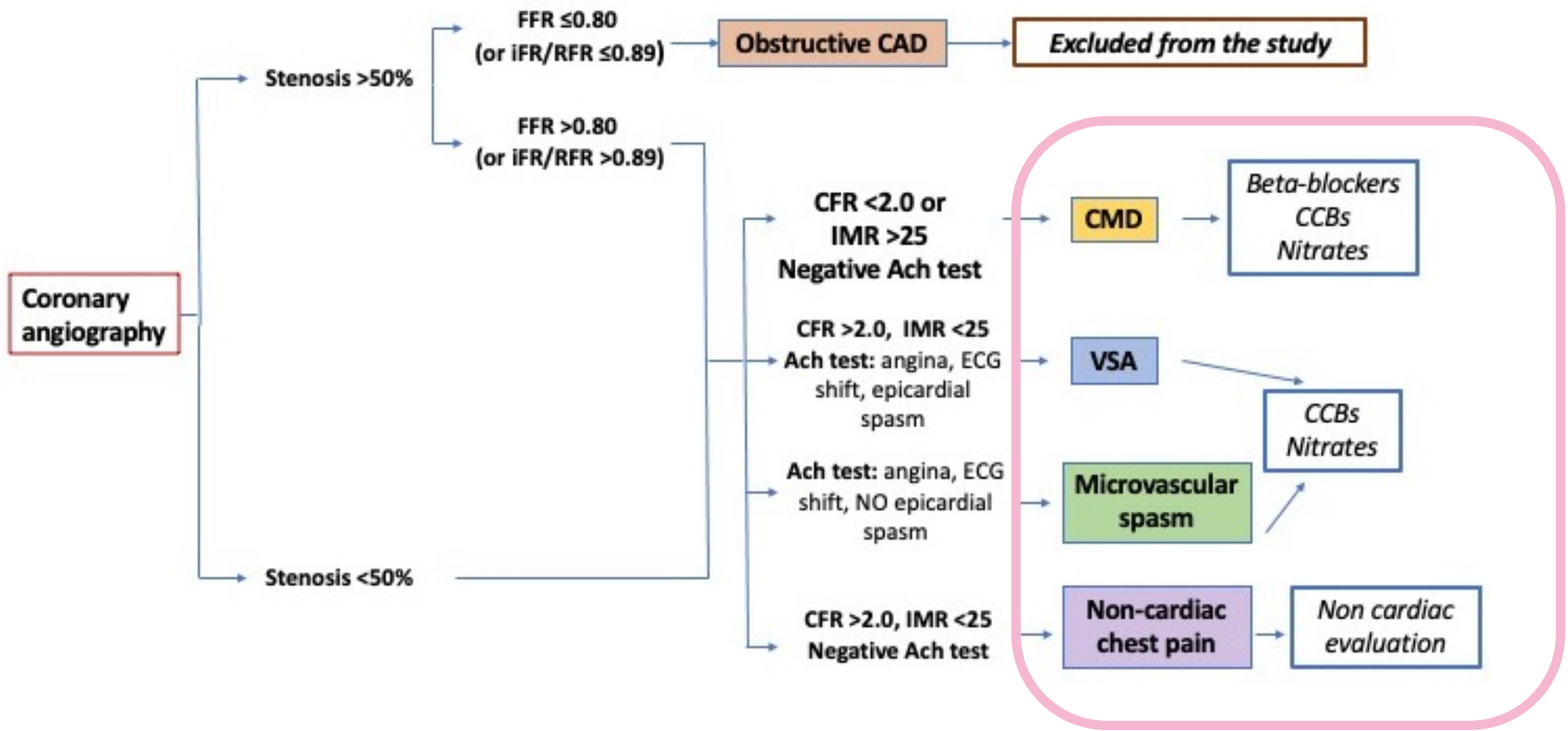
Treatment Schedule



Case-Based Presentation 1: INOCA - How to Diagnose and Treat

Coronary Microvascular Dysfunction (CMD)

CLINICAL PRESENTATION

- ♀, 51 years old

- **Risk factors for Cardiovascular Disease:** Hypertension, Dyslipidaemia, Family History for CAD

METABOLIC STATUS
Patient Journey

- **BMI** 26.7
- **Fasting blood glucose** 92 mg/dL
- **LDL-c** 154 mg/dL

BLOOD TEST

CLINICAL PRESENTATION
Patient Journey

- **Gennaio 2020** Dolore toracico da sforzo CCS 2
- Marzo 2020 1 visita presso medico di base che le consiglia *ansiolitici*
- Settembre 2020 2 visita medico di base persiste dolore toracico da sforzi moderati > medico di base prescrive *visita cardiologica*
- Dicembre 2020 visita cardiologica che prescrive ecocardiogramma e TDS ed inizia empiricamente la seguente terapia : Diltiazem 60 mg x3/die, Olmesartan 20 mg/die
- Giugno 2021 TDS positivo per ischemia per sintomi ed ECG
- Settembre 2021 seconda visita cardiologo paziente ancora sintomatica ora per minimi sforzi nonostante terapia medica per angina CCS 3 . Riferita presso nostro centro per coro

- **December 2021:** CCS4. Arruolata in **INOCA- IT Registry**

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ANGINA CCS IV

EQ-5D-5L

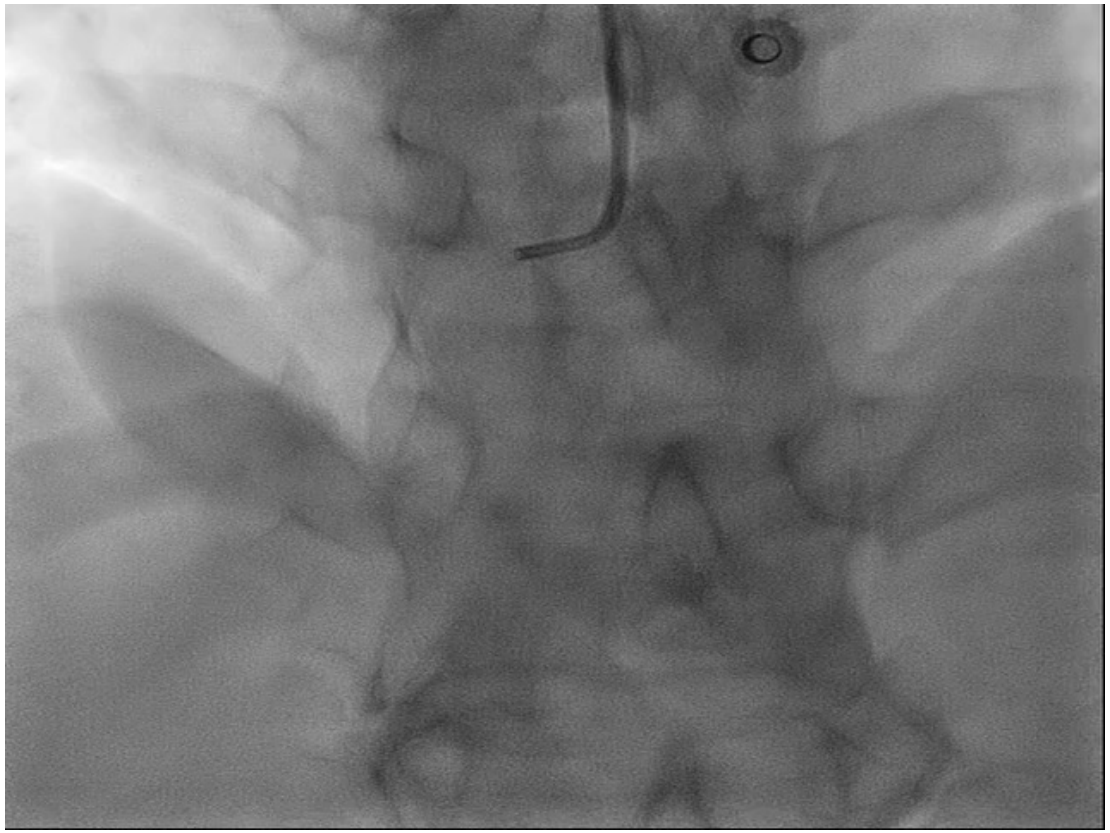
Questionario sulla Salute

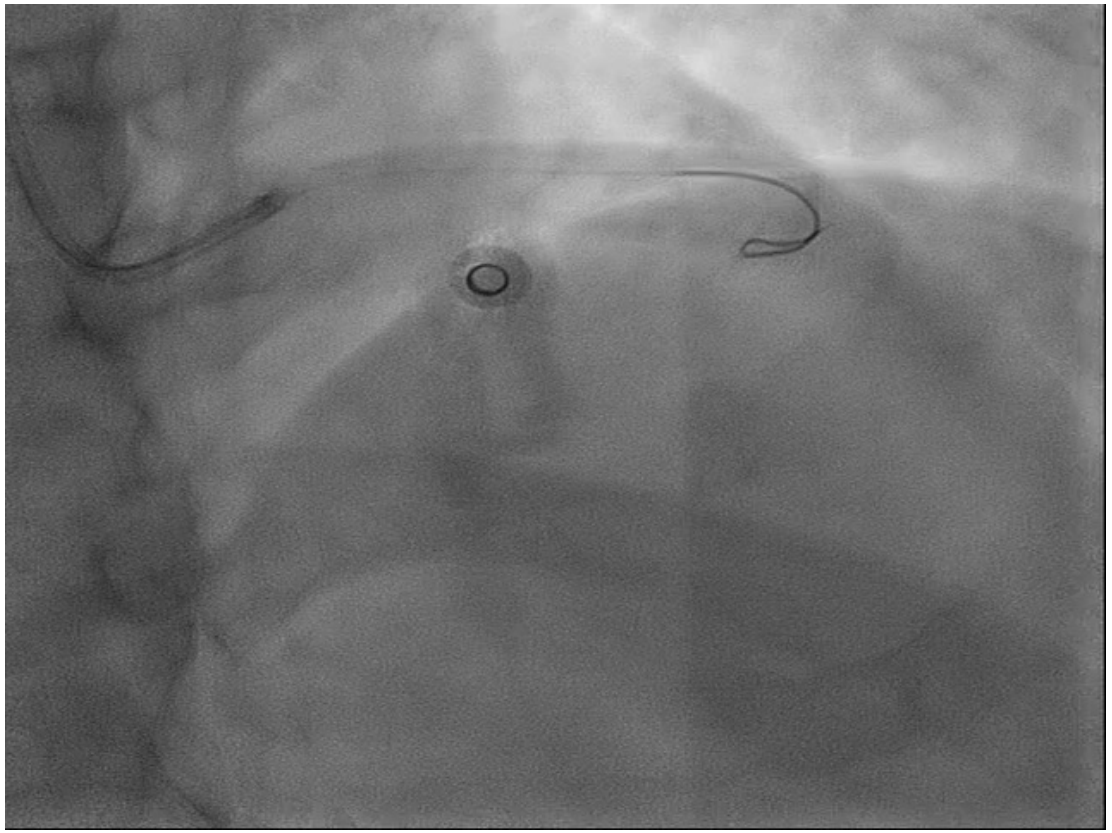
Versione italiana per l'Italia

(Italian version for Italy)

VAS score: 50%

CORONARY ANGIOGRAPHY





Coronary function testing: Diagnostic guidewire and Adenosine test

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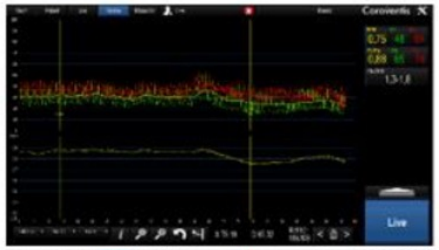
- FFR, RFR, Pd/Pa
- Pullback

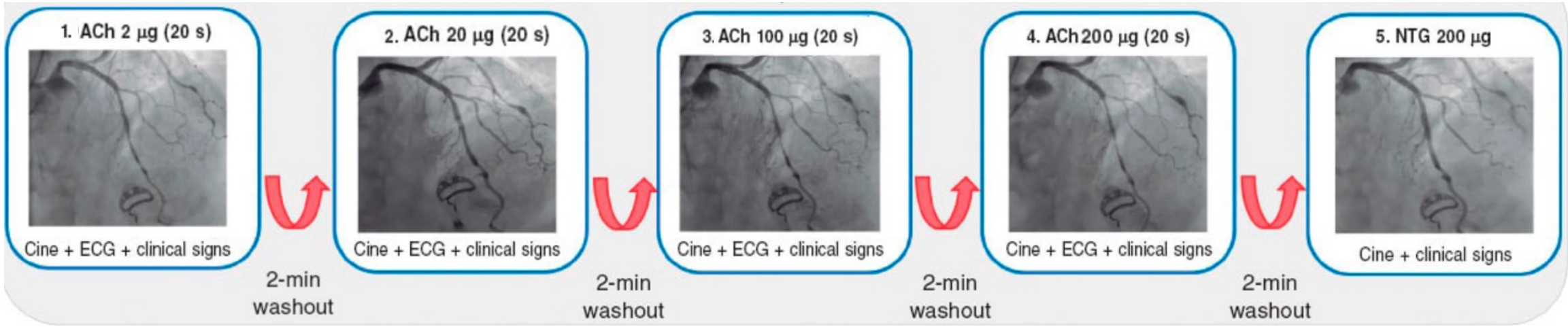


Microvascular assessment

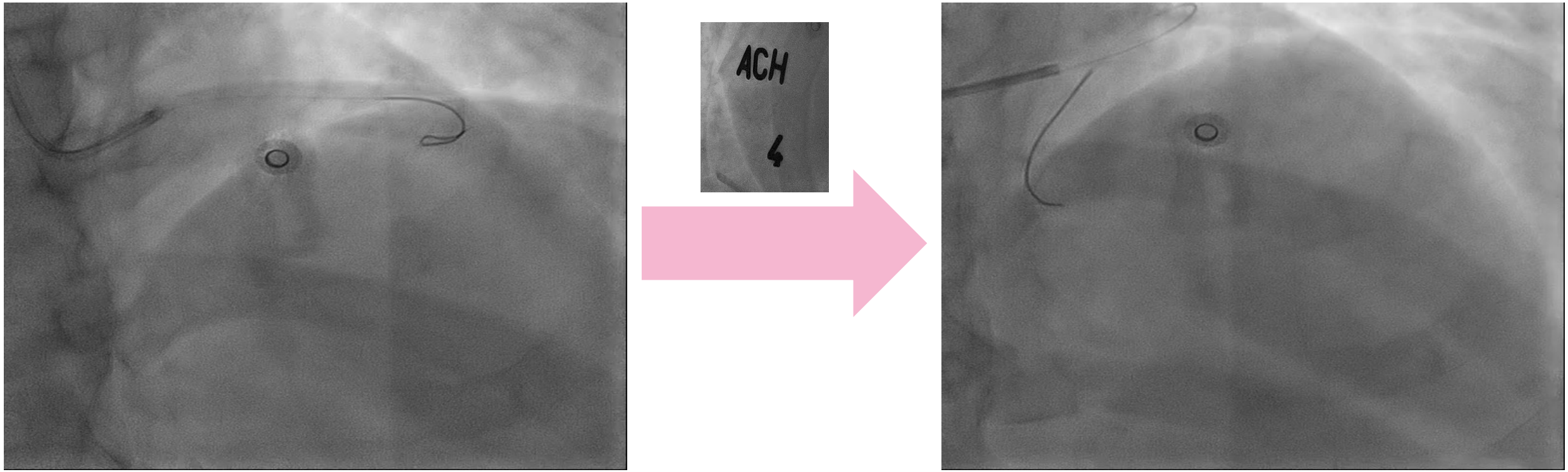
- IMR, RRR
- CFR, PB-CFR
- Absolute Flow/Resistance

CORONARY FUNCTION TESTING: CMD

Acetylcholine Test



ACETYLCHOLINE PROVOCATION TEST: NEGATIVE



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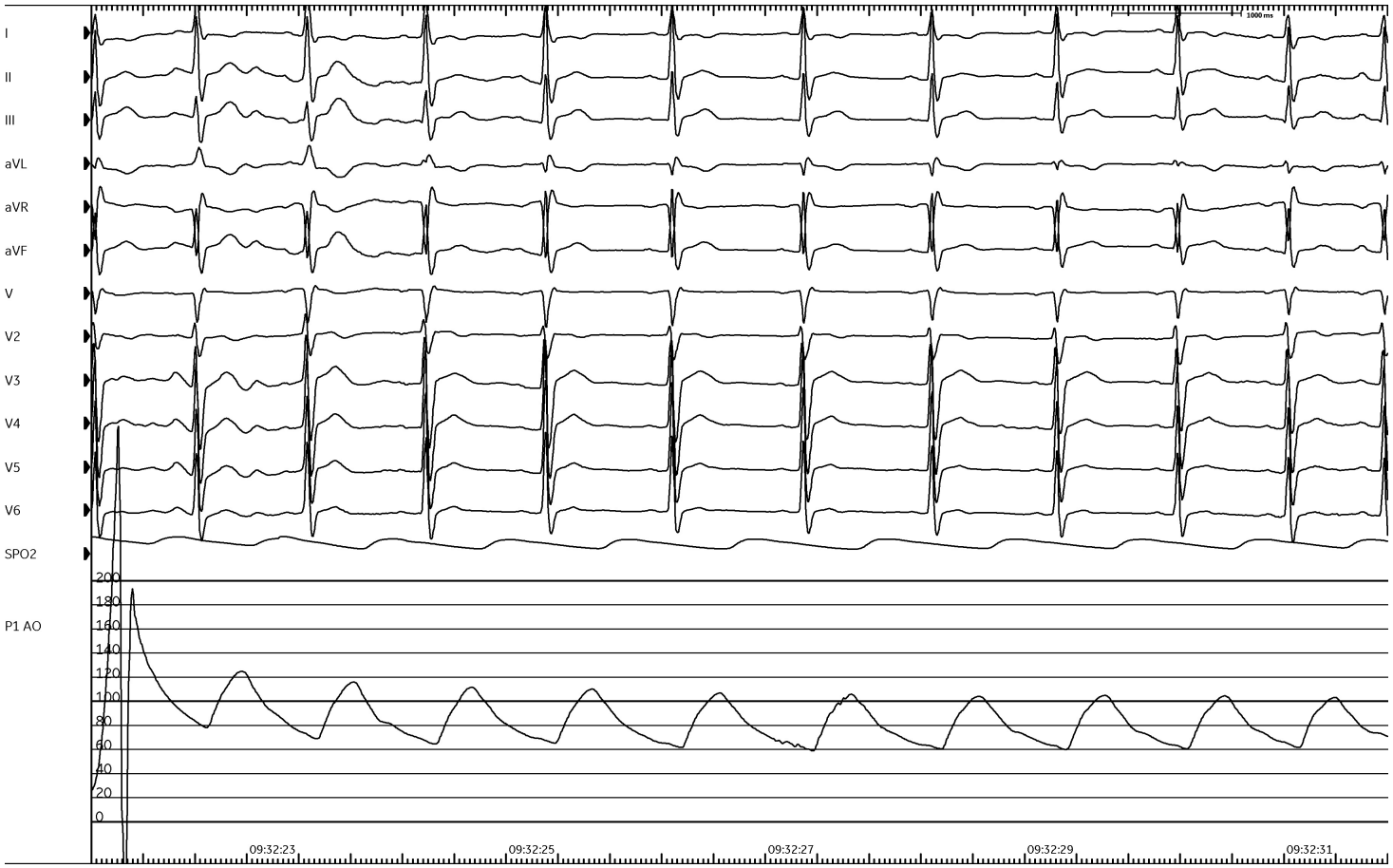


MANAGEMENT

- **Diagnosis:** Coronary Microvascular Dysfunction
- **Lifestyle modification, diet, physical activity , risk factors modification**
- **Changes to Medication:**

Diltiazem

Nebivololo 5 mg/die
Ranolazina 350 1cpx2die
Rosuvastatin 10 mg

One Month Follow Up

- **Diagnosis:** Coronary Microvascular Dysfunction

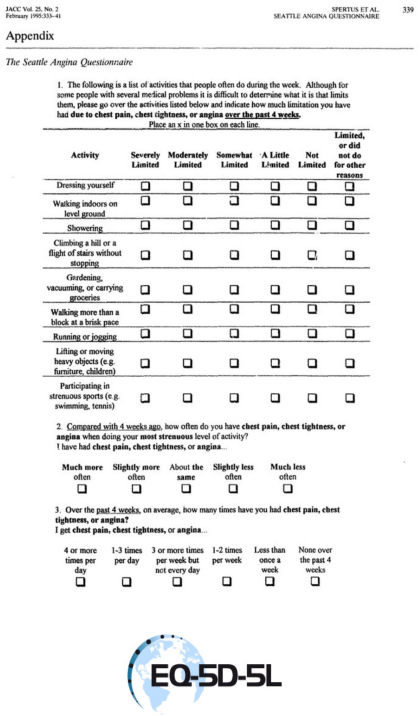
  Angina status : From CCS4 to CCS2 EKG sinus rythm HR 70 bpm AP 130/80 mmHG

- **Changes to Medication:**

Nebivololo 5 mg/die
Ranolazina 350 1cpx2die
Rosuvastatin 10 mg

Nebivololo 10 mg/die
Ranolazina 500 1cpx2die
Rosuvastatin 10 mg

One Year FOLLOW-UP



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SEATTLE ANGINA QUESTIONNAIRE

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Appendix

The Seattle Angina Questionnaire

1. The following is a list of activities that people often do during the week. Although for some people with several medical problems it is difficult to determine what it is that limits them, please go over the activities listed below and indicate how much limitation you have had **due to chest pain, chest tightness, or angina over the past 4 weeks.**

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☐	☐	☐	☐	☐	☐

EQ-5D-5L

Questionario sulla Salute

Versione italiana per l'Italia

(Italian version for Italy)

Physical Limitation Domain: 38 ➡ 44
Angina Stability Domain: 3➡ 2
Angina Frequency Domain: 9 ➡9
Treatment Satisfaction Domain: 12 ➡16
Quality of Life Domain: 5 ➡ 10

(A higher subscale score represents fewer functional limitations or patient is more satisfied)

VAS score: 50%➡ 90%

ANGINA CCS IV ➡ CCS I

LDL C 50 mg/dL .Good AP control. Regular physical activity. BMI 22

Nebivololo 10 mg/die Ranolazina 500 1cpx2die Rosuvasttain a10 mg /dL

Case-Based Presentation 2: INOCA - How to Diagnose and Treat

Vasospastic Angina (VA)

CLINICAL PRESENTATION

- ♂, 38 years old

- **Risk factors for Cardiovascular Disease:** type 1 Diabetes, Dyslipidaemia
- **Comorbidities:** Sarcoidosis, GERD, Anxiety Disorder, Asthma

METABOLIC STATUS
Patient Journey

- **BMI** 24.8
- **Fasting blood glucose** **122** mg/dL (Type 1 Diabetes)
- **LDL-c** 52 mg/dL

BLOOD TEST

CLINICAL PRESENTATION

- **Cardiovascular HIstory:**

  - 2019 angina da sforzo -> RCA PCI

  - 2022 episodi di dolore toracico a riposo di insorgenza mattutina con limitazione attività quotidiane e lavorative . Si ricovera per coro ed ev

- **Baseline Medication**: Acetylsalicylic Acid 100 mg/die, Ticagrelor 90 mgx2/die, Rosuvastatin+Ezetimibe 20+10 mg/die, Diltiazem 30 mgx2/die, Insulin, Omeprazole 40 mg/die

Ischemia in patients with non-obstructive disease (INOCA) in Italy

INOCA IT Multicenter Registry. (RF-2019-12369486)

Enrolment

Acronimo RF-2019-12369486 "Ischemia in patients with non-obstructive disease (INOCA) in Italy INOCA IT Multicenter registry"

FOGLIO INFORMATIVO,
DICHIARAZIONE DI CONSENSO
E INFORMATIVA PRIVACY
per un paziente adulto capace di dare personalmente il consenso

Modulo di consenso informato: Versione 3.0 del 12/07//2021

Parte 1

Gentile signora/e,

1) In questo Istituto Le viene proposto di partecipare ad una ricerca clinica sul ruolo d
parametri di funzionalità (fisiologia) del microcircolo coronarico per l'identificazione e la caratt
quei pazienti che presentino ischemia cardiaca in assenza di patologia ostruttiva delle arterie
condizione definita dal termine ischemia non ostruttiva delle arterie coronarie (INOCA). Qu
legato ad una varietà di disturbi funzionali del microcircolo coronarico, si riscontra in circ
pazienti che vengono sottoposti a coronarografia nel sospetto di cardiopatia ischemica, i
donne di mezza età, e conferisce un aumentato rischio di eventi cardiovascolari avversi
miocardico e scompenso cardiaco), oltre ad avere un significativo impatto negativo sulla
stato attuale, la gestione terapeutica dei pazienti affetti da INOCA è controversa, tutt
emerge che un trattamento specifico, guidato dalla valutazione invasiva dei parame
microcircolo coronarico, può ridurre i sintomi e migliorare la qualità di vita di quest
questa ricerca potrebbero aiutare, quindi, a riconoscere e caratterizzare la disfunzione
dell'INOCA e garantire l'accesso ad una terapia individualizzata con lo scopo di
prognosi di tale patologia.
Il titolo dello studio è: "Ischemia in pazienti con malattia coronarica non ostruttiva
Registro Multicentrico INOCA IT (RF-2019-12369486).
Questo studio è nazionale, prospettico, interventistico, multicentrico, non rando
aperto che si propone di arruolare in 3 centri italiani 200 pazienti consecutivi di
con sospetta cardiopatia ischemica cronica in assenza di coronaropatia ostrutti
clinicamente indicata.
Lo studio è promosso dall'IRCCS San Raffaele (centro coordinatore) e finan
Per svolgere tale ricerca abbiamo bisogno della collaborazione e della disp
soddisfino i requisiti scientifici idonei alla valutazione che verrà eseg
partecipare a questa ricerca sulla quale Lei ha già avuto informazioni det
studio.
Prima, però, che Lei prenda la decisione di accettare o rifiutare di par
attenzione, prendendo tutto il tempo che Le necessita, queste pagine
avesse ben compreso o avesse bisogno di ulteriori precisazioni. I
decidere può chiedere un parere ai suoi familiari o ad un suo medic

2) Questa ricerca si propone come obiettivo generale di:
Migliorare la conoscenza della malattia del paziente.
In particolare, con la ricerca che qui Le presentiamo,
caratterizzare i pazienti che presentino ischemia cardiaca in
coronarie. Questi pazienti possono presentare una varietà di
che complessivamente conferiscono un aumentato rischio di

Appendix

The Seattle Angina Questionnaire

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ANGINA CCS IV

EQ-5D-5L

Questionario sulla Salute

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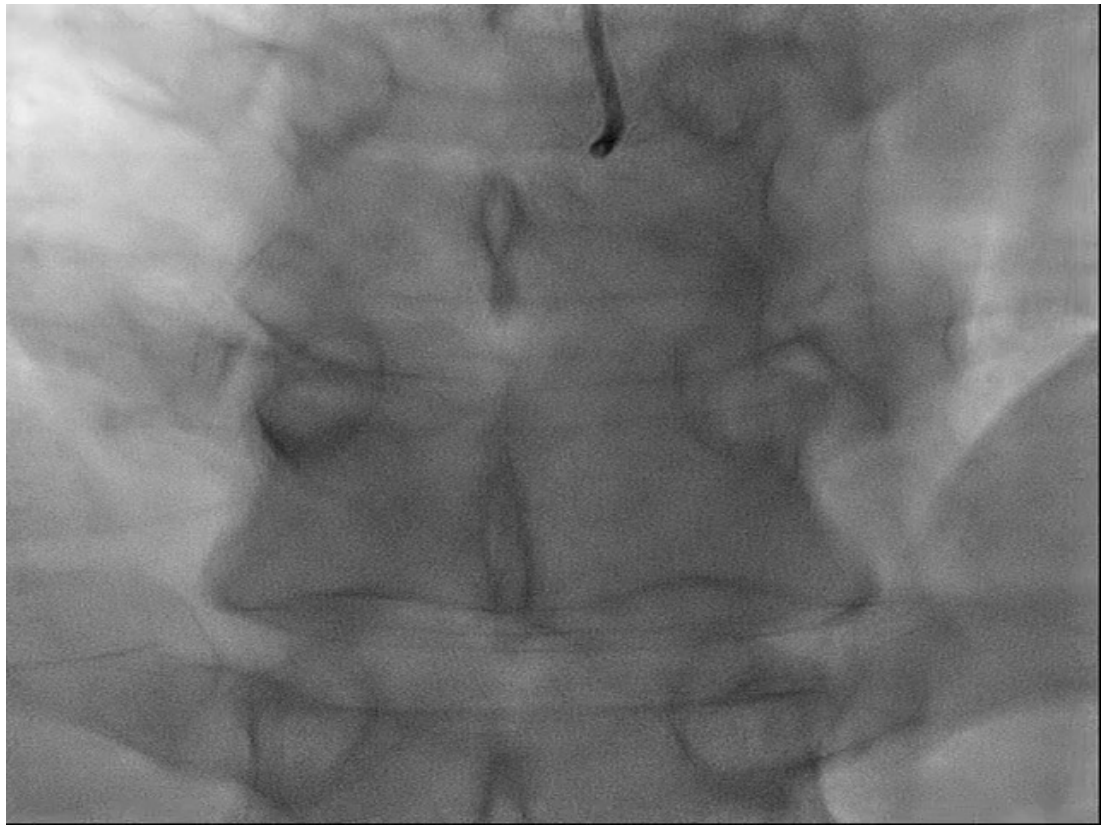
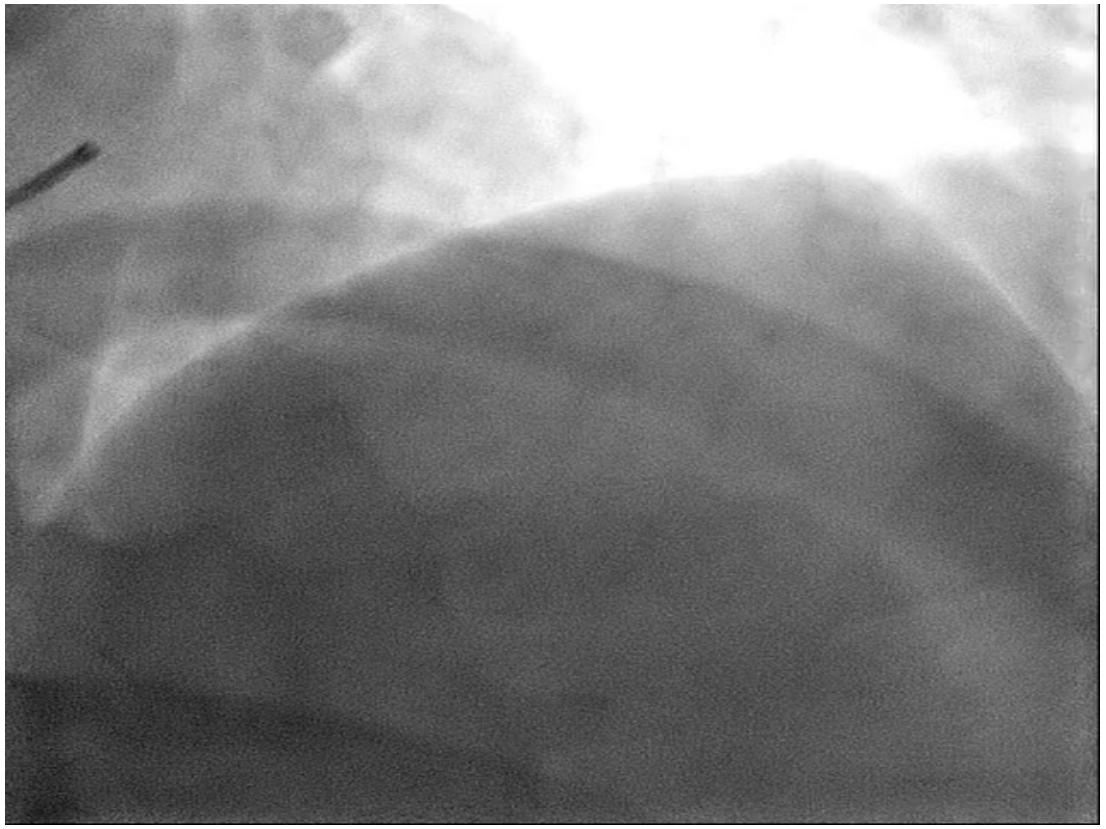
VAS score: 50%

CORONARY ANGIOGRAPHY





Arruolato in **INOCA- IT Registry**

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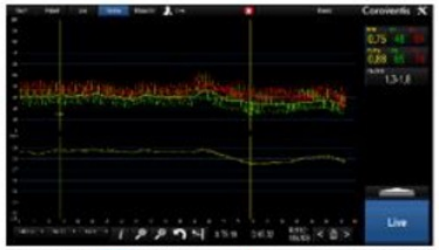

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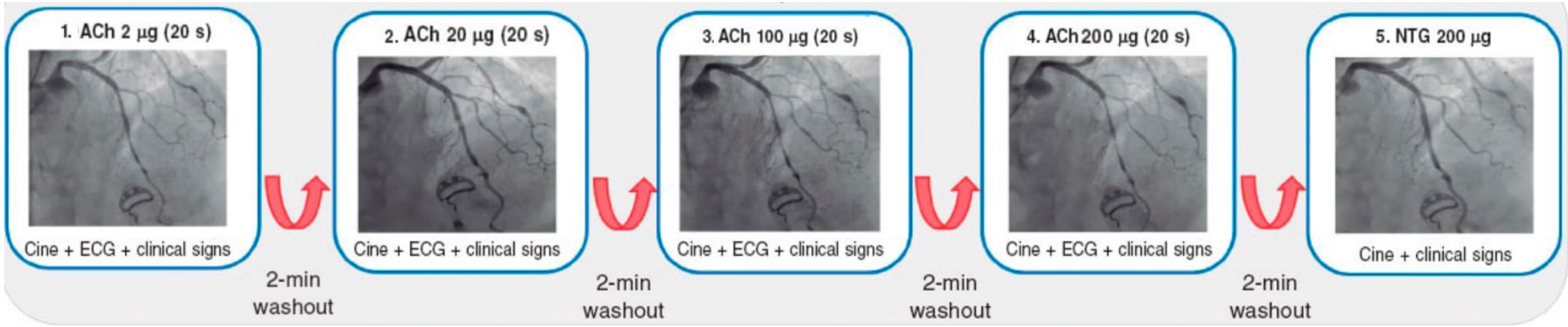
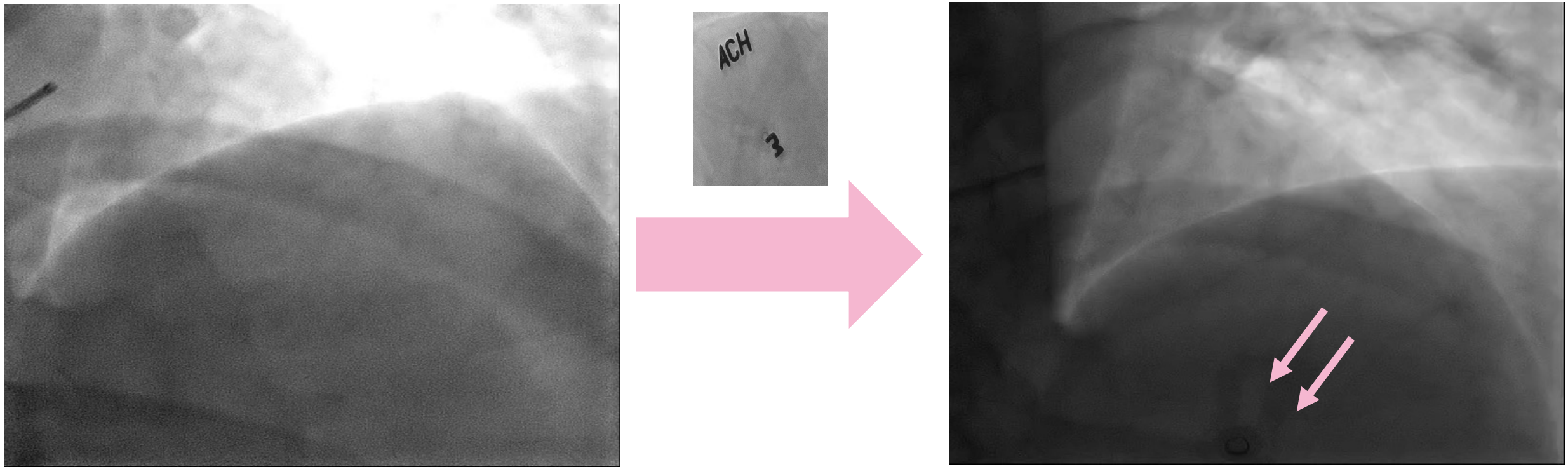


ACETYLCHOLINE PROVOCATION TEST: POSITIVE



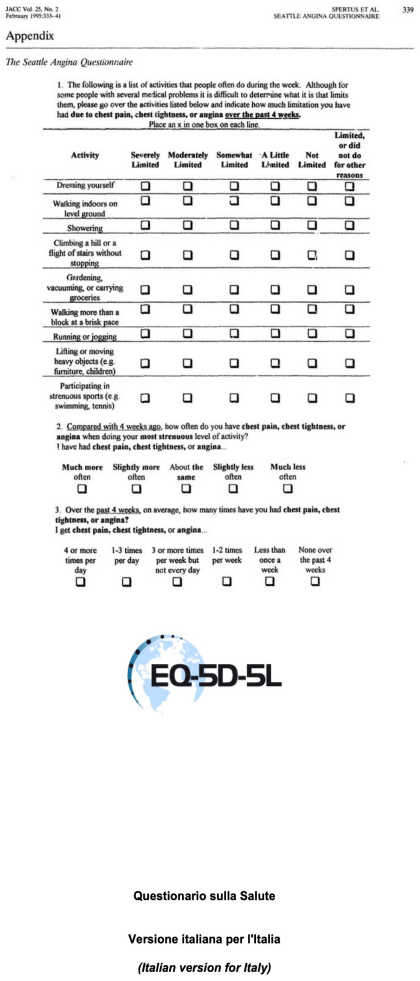
ACETYLCHOLINE PROVOCATION TEST: POSITIVE

MANAGEMENT

- **Diagnosis:** Vasospastic Angina
- **Changes to Medication:**

Uptitration to Diltiazem 120 mg x2/die

One Year FOLLOW-UP



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Physical Limitation Domain: 45 ➡ 48
Angina Stability Domain: 3➡ 5
Angina Frequency Domain: 9 ➡11
Treatment Satisfaction Domain: 16 ➡17
Quality of Life Domain: 6 ➡ 10

(A higher subscale score represents fewer functional limitations or patient is more satisfied)

VAS score: 50% ➡ 70%

ANGINA CCS IV ➡ CCS 0

Conclusioni I

- **Strategie diagnostiche invasive** che utilizzano la coronarografia e procedure diagnostiche interventistiche dovrebbero essere implementate per poter formulare una diagnosi accurata dell' endotipo di INOCA in presenza di CAD non ostruttiva

→ "Full Physiology" con guide /caterer diagnostici e misurazione parametri di flusso e pressione

→ Test di vasoreattività coronarica- test Acetilcolina

Conclusioni II

Un approccio stratificato per la gestione dei pazienti of INOCA è necessario

- Tailored counselling sullo stile di vita e gestione fattori di rischio
- Tailored therapy Uso farmaci anti anginosi a secondo endotipo INOCA per migliorare la sintomatologia e la qualità della vita

Sviluppo di progetti di ricerca

- per migliorare la comprensione della fisiopatologia
- Sviluppare nuove terapie

Thanks for your attention

 chieffo.alaide@hsr.it

 @alaide_chief

 Dra_chieffo

 Linkedin.com/in/alaide-chieffo-922ba831