

**FROM TREATMENT OF CHRONIC SYMPTOMS
TO
PREVENTION OF ACUTE EVENTS**

FROM TREATMENT OF CHRONIC SYMPTOMS TO PREVENTION OF ACUTE EVENTS

- ◆ Existing cardiac therapies focus on the reduction of chronic cardiac symptoms
- ◆ Future treatments for Vulnerable Plaque will focus on the prevention of acute events.

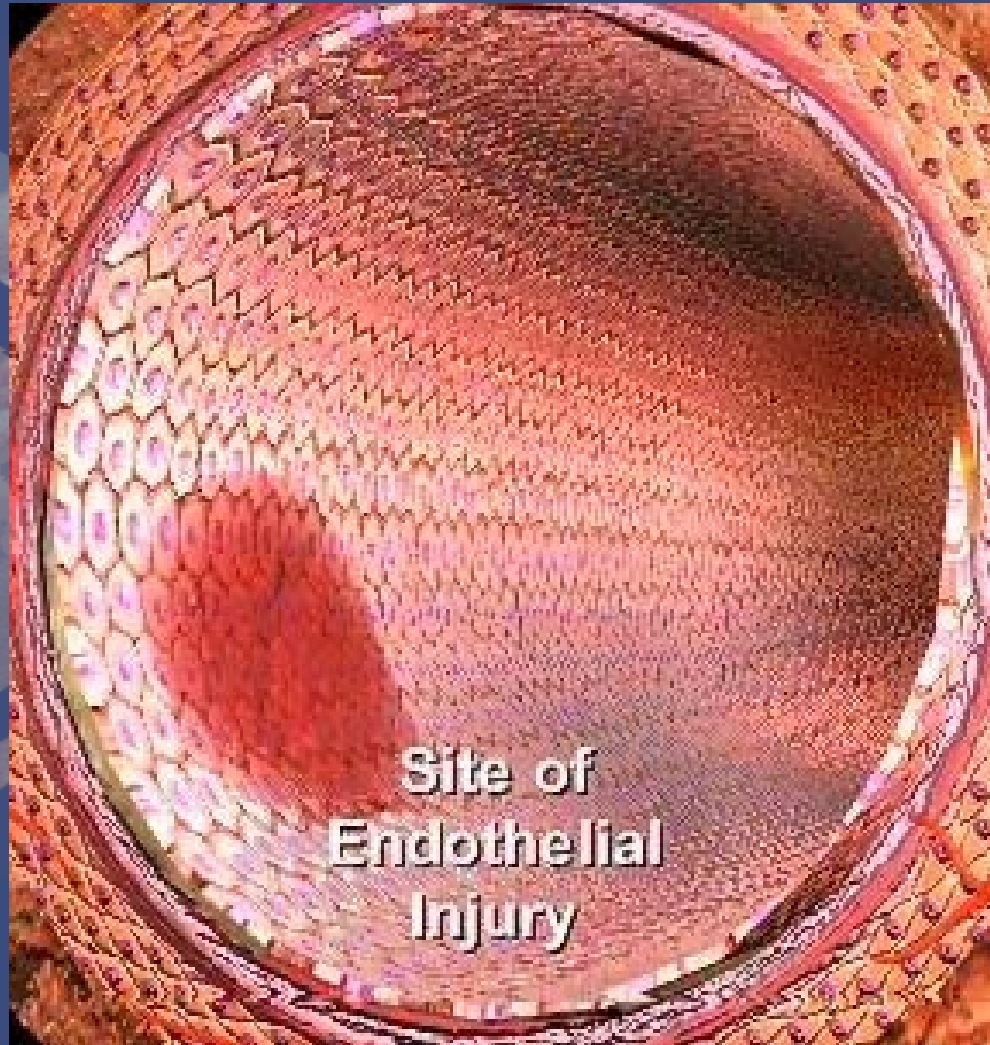


What is Vulnerable Plaque ?

Development of atherosclerosis

(underlying mechanisms of the disease)

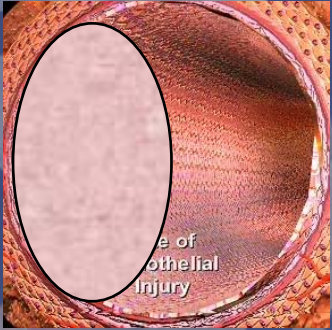
These plaques often
do **NOT** cause
significant stenoses



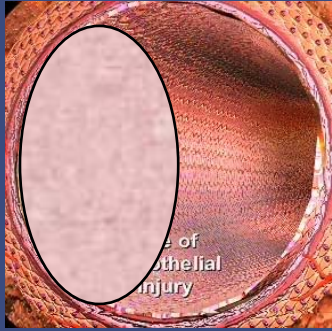


V Plaque

Occlusive artery disease



40% Narrowing



Family History

Genetic

Diabetes

Smoking

Cholesterol

Alcohol

?

High Inflammation

Thin Cap

=

High risk of rupture

MI - Death

Low Inflammation

Stable Cap

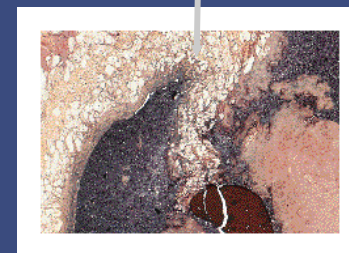
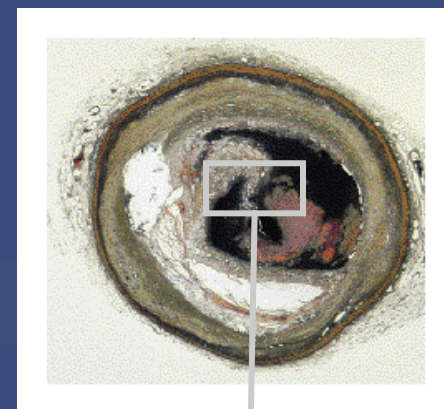
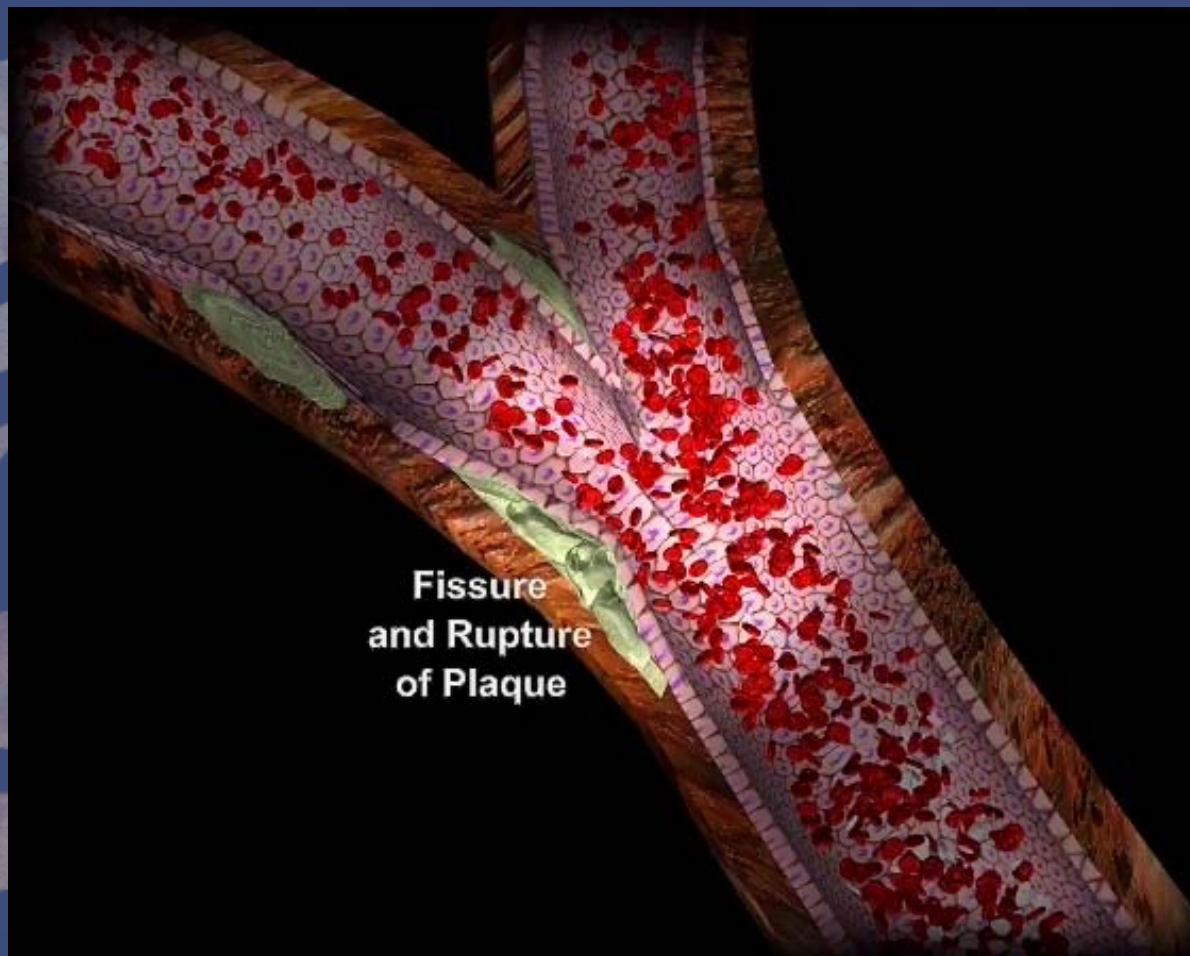
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Low risk of rupture

Stable Angina – 95%

Flow limiting plaque

Rupture of plaques that initially caused insignificant stenoses



Vulnerable Plaque

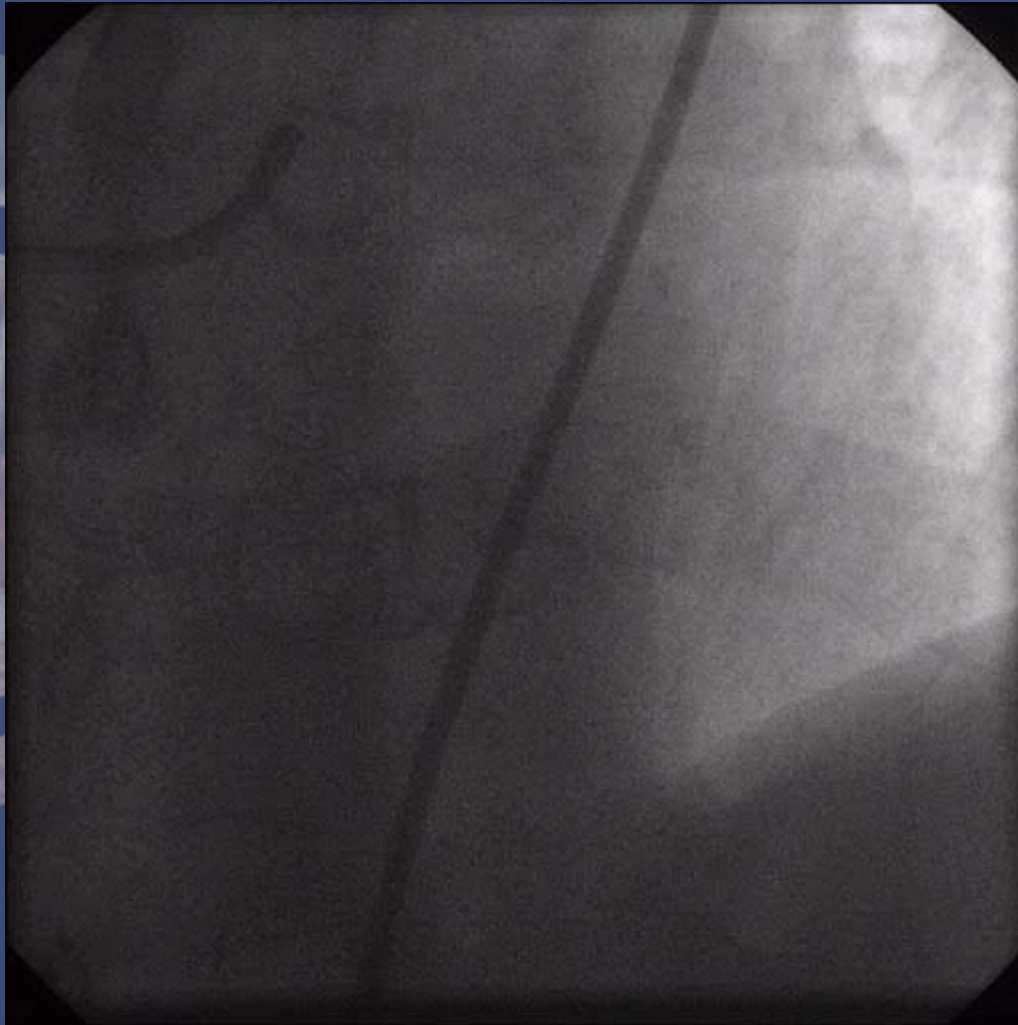
A new Coronary treatment Challenge

- ◆ Arterial Narrowing – Intended Use
 - To deliver a focal therapy to a stenosed flow limiting lesions within an artery to reduce or eliminate chronic cardiac symptoms
- ◆ Vulnerable Plaque – Intended Use
 - To deliver a therapy to an arterial lesion to prevent a life threatening acute MI



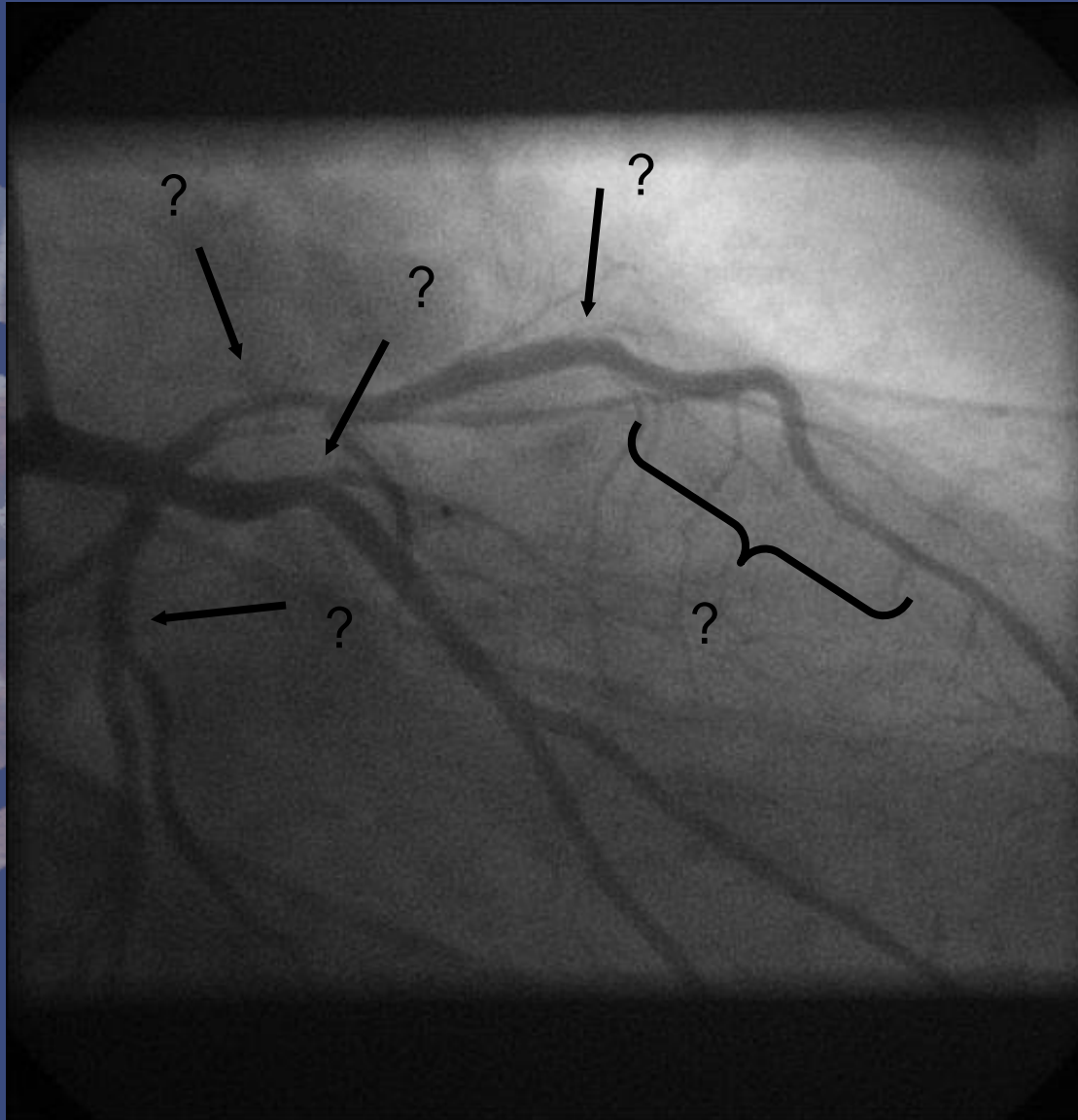
Existing Diagnosis

What is the current standard for diagnosing atherosclerosis in the cathlab?



Are we missing
something...?

Yes we are!

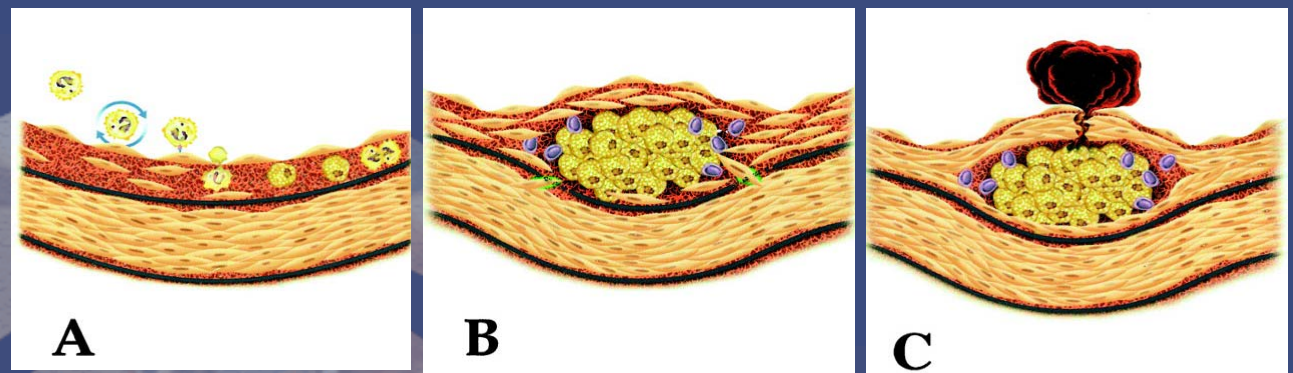




Intra-coronary Thermography

Scientific principal

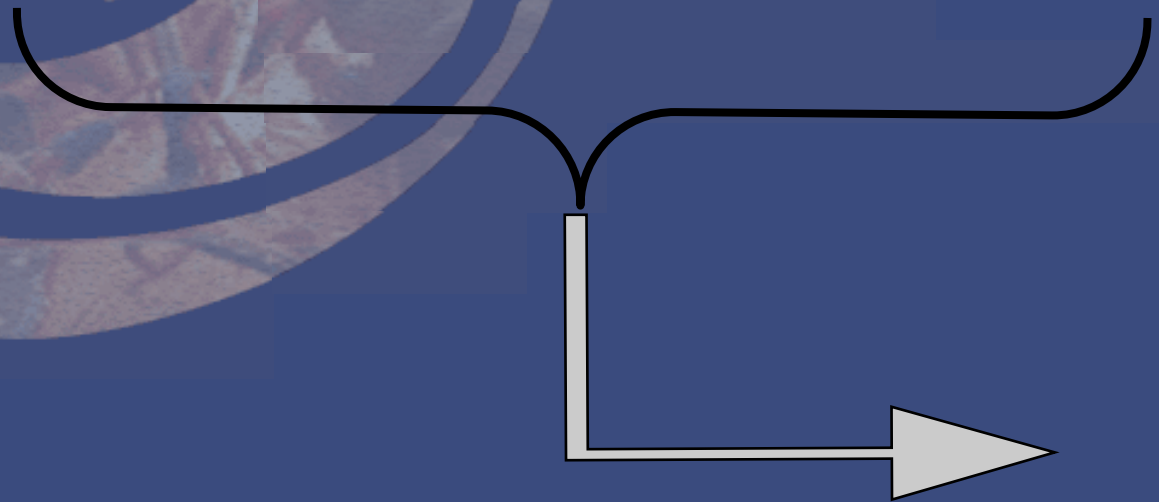
We're missing out on functionality!



A
Macrophage entering the vessel wall

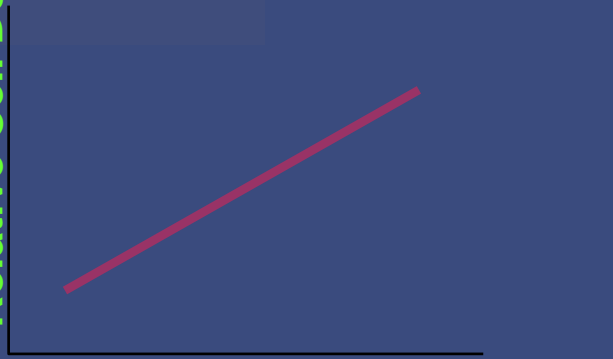
B
Development of plaque

C
Rupture of plaque with induction of thrombus



Relative Cell Density

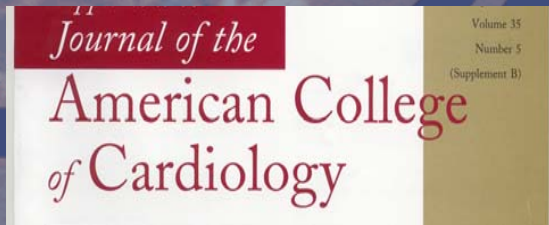
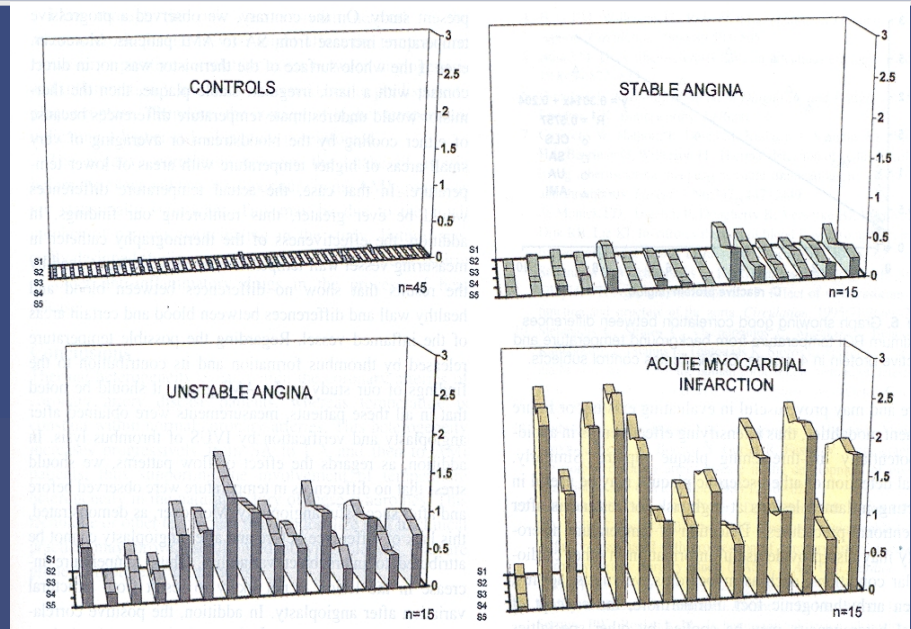
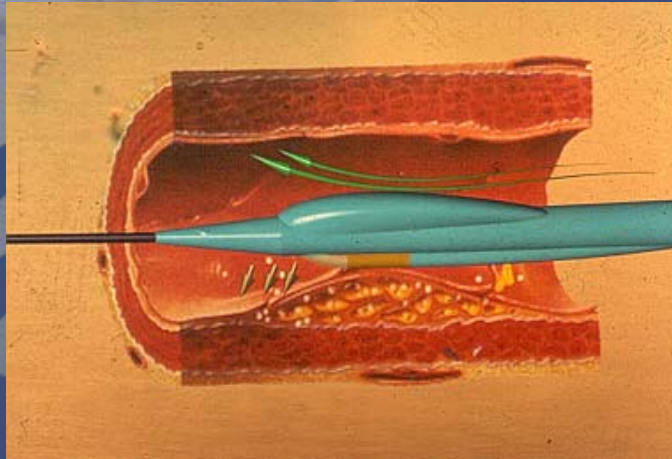
Temperature difference



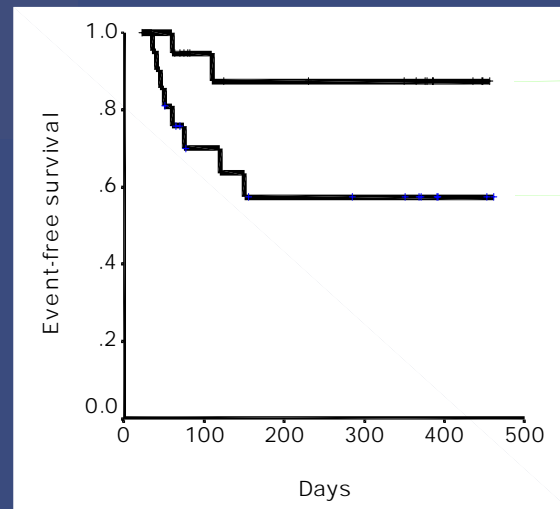
In Vivo thermography – first results



Stefanadis et al., *Circulation* 1999, 99: 1965-1971



Stefanadis et al., *J Am Coll Cardiol*, June 2001



No temperature difference

Temperature difference

Device Description

The Thermocore Medical Systems Thermosense System consists of :

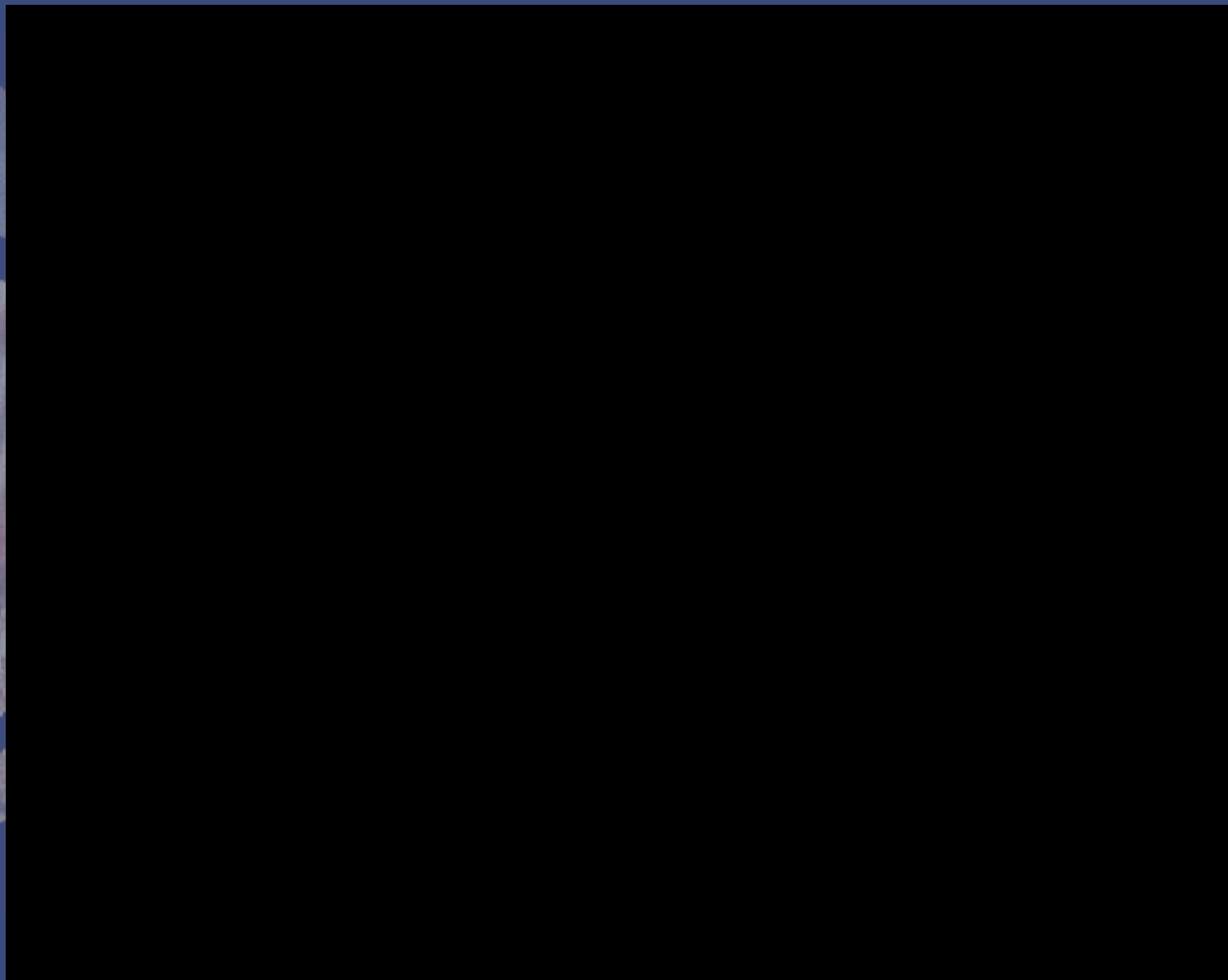
Thermosense™ Catheter

Thermosense™ Console

Thermosense™ Pullback

The following video outlines the main features of the device

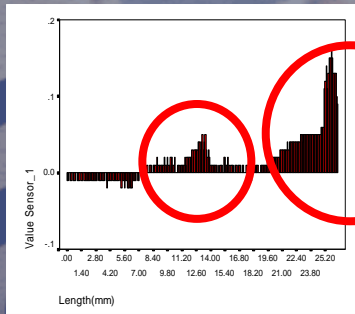
Device Description



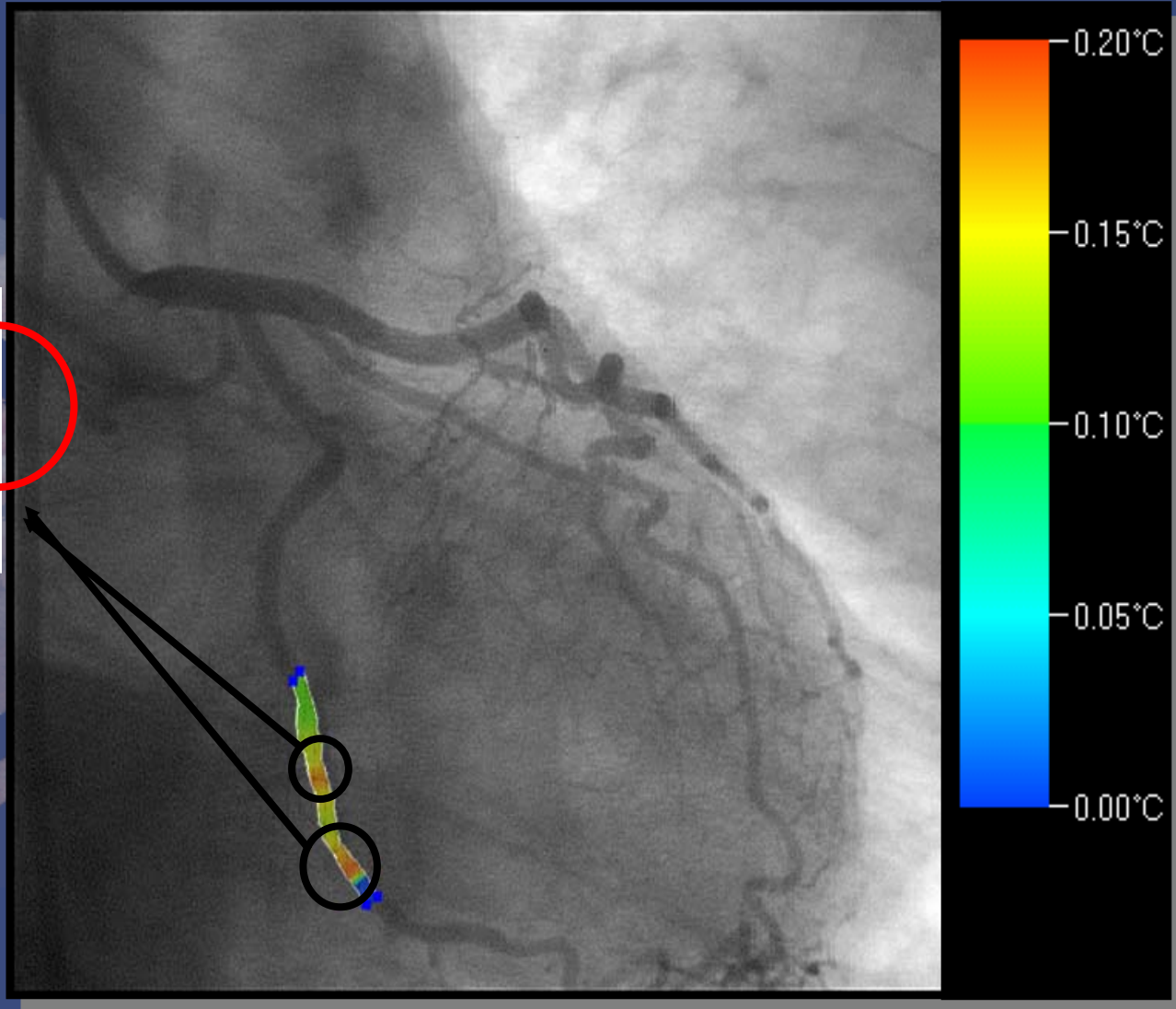


Thermocore UK Ltd
Initial clinical experience with CE marked system

Male, 67 years, stable coronary artery disease



2
temperature
bumps



Temperature overlay

Intra-coronary Thermography

- The aim of intra coronary thermography is to diagnose the presence of active inflammatory plaque that are prone to rupture (vulnerable plaque)
- The secondary aim is to stratify the vulnerable plaque into bands related to the probability of events occurring within a specified time window

How did we get there?

- Medical Device Directive 93/42/EEC
- Annex II
- Quality Standards EN ISO 9000/ EN ISO 13485
- Essential Requirements
- Risk Analysis
- Standards
- Clinical Evaluation
- Declaration of Conformance

CE Mark Approval

- Class III Design Examination (LRQA) Catheter
 - Design examination certificate for a class III device under annex II of the Medical Devices Directive 93/42/EEC
- Class IIb Electromedical (LRQA) Console + Pullback
 - Technical file review
- Quality System Approval (LRQA)
 - Development and management of manufacture of medical device systems for cardio-vascular thermography
 - ISO 9001 / ISO 13485
- Manufacturing Subcontractors
 - Sterile Single Use Catheter - Occam International
 - Electromedical Console/Pullback – TriVirix

Harmonised Standards

“Harmonised Standard”

- a standard produced under a mandate from the European Commission by one of the European standardization bodies and which has its reference published in the Official Journal of the European Communities.

Compliance with a Harmonised Standard carries with it an automatic presumption of conformity with the Essential Requirements.

Example - Harmonised Standard for Risk Analysis:
ISO 14971-1:1998 Medical Devices - Risk Management -
Part 1: Application of risk analysis

Preferential Order of Standards:

- ◆ Harmonised Standards
- ◆ Non-harmonised European Standard (EN, ENV, prEN) or Harmonisation Document, (HD)
- ◆ ISO/IEC standard
- ◆ National standard of Member State
- ◆ National standard of third country
- ◆ Manufacturer's specification (may even exceed Harmonised Standard requirement)

Verification and Validation

Catheter

EN ISO 10555-1: Sterile, single-use intra-vascular catheter

Biological Evaluation

EN ISO 10993-1: Biological evaluation of medical devices
FDA Guidance

Clinical Evaluation

EN540 / MDD 93/42/EEC, Two clinical trials Antwerp /
Rotterdam

Sterilisation

EN552 - Gamma Irradiation 25K Gy – SAL 10⁻⁶

Verification and Validation

Electromedical / Software

EN 60601-1

1-1-1 Electro medical systems

1-1-2 Electromagnetic compatibility

1-1-4 Programmable Electrical Medical Systems (software)

FDA Guidance

General Principles of Software Validation

Testing and Certification by BSI

EN 60601-1

EN 60601-1-1

Testing and Certification

EN 60601-1-2

Clinical Safety Results

Antwerp (n = 33, control trial group n = 50)

- Patients scheduled for a diagnostic procedure found to have no significant stenoses
- No MACE during procedure
- No MACE during 14 Day follow-up
- No ECG changes during 14 Day follow-up
- No significant blood chemistry differences

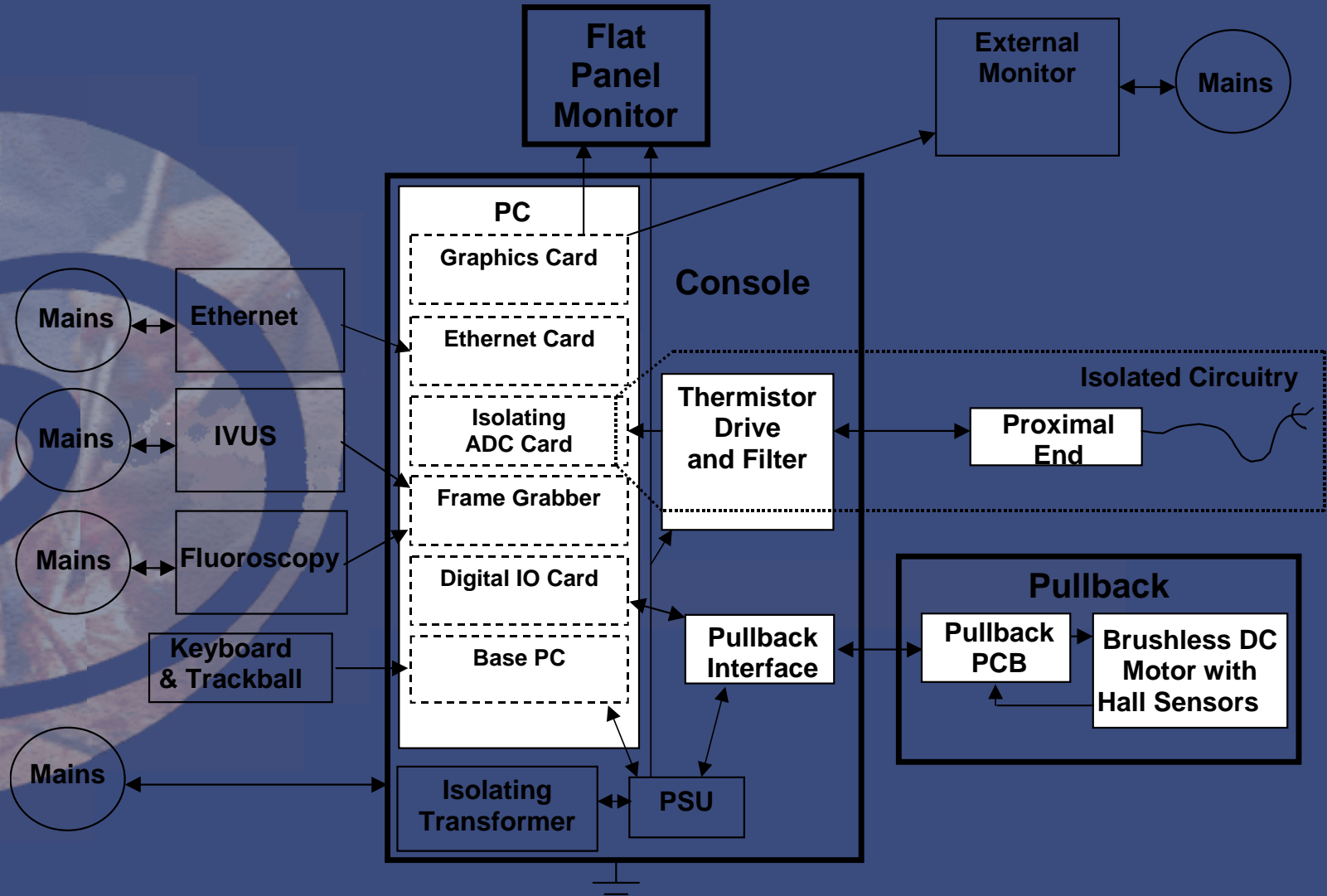
Rotterdam (n = 9)

- Patients undergoing PCI
- No MACE during procedure
- No MACE during 14 Day follow-up



Electronic Design

System Description



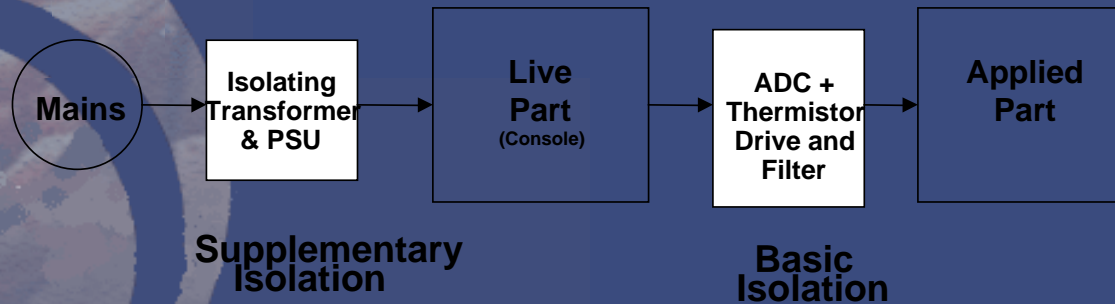
Safety Overview - Patient Safety

- Isolation between the patient and Live/Mains provided so that the patient leakage levels are within the requirements of IEC 60601 for a type CF Defibrillation Proof Applied Part.
- The Console provides all the required isolation so that there is no reliance on the insulation layer around the electrical parts of the Catheter. The isolation is as follows:
 - Isolation against Mains consist of two stages so that the system is protected against a single failure.
 - The first layer of isolation provided by the ADC card in parallel with the Thermistor Drive and Filter PCB and designated as Basic Isolation. Under IEC 60601 this means a dielectric strength greater than 1500V for protection against Mains voltages.

Safety Overview - Patient Safety

- The second layer provided by the isolating transformer and PSU that provides power for the Instrumentation. This is designated as Supplementary Isolation and provides at least 2500V isolation against Mains voltages.
- Isolation against Live voltages in the Console (-12VDC to +12VDC) provided by the ADC card and Thermistor Drive and Filter PCB in parallel. These act as Double Isolation against the Live voltages. Under IEC 60601 this means testing to 500V.
- It is the responsibility of the User (authority responsible for the maintenance of the equipment) to ensure that the system as a whole meets [IEC 60601] should they attach other devices onto the Instrumentation (such as IVUS). This is noted in the documentation for the Instrumentation.

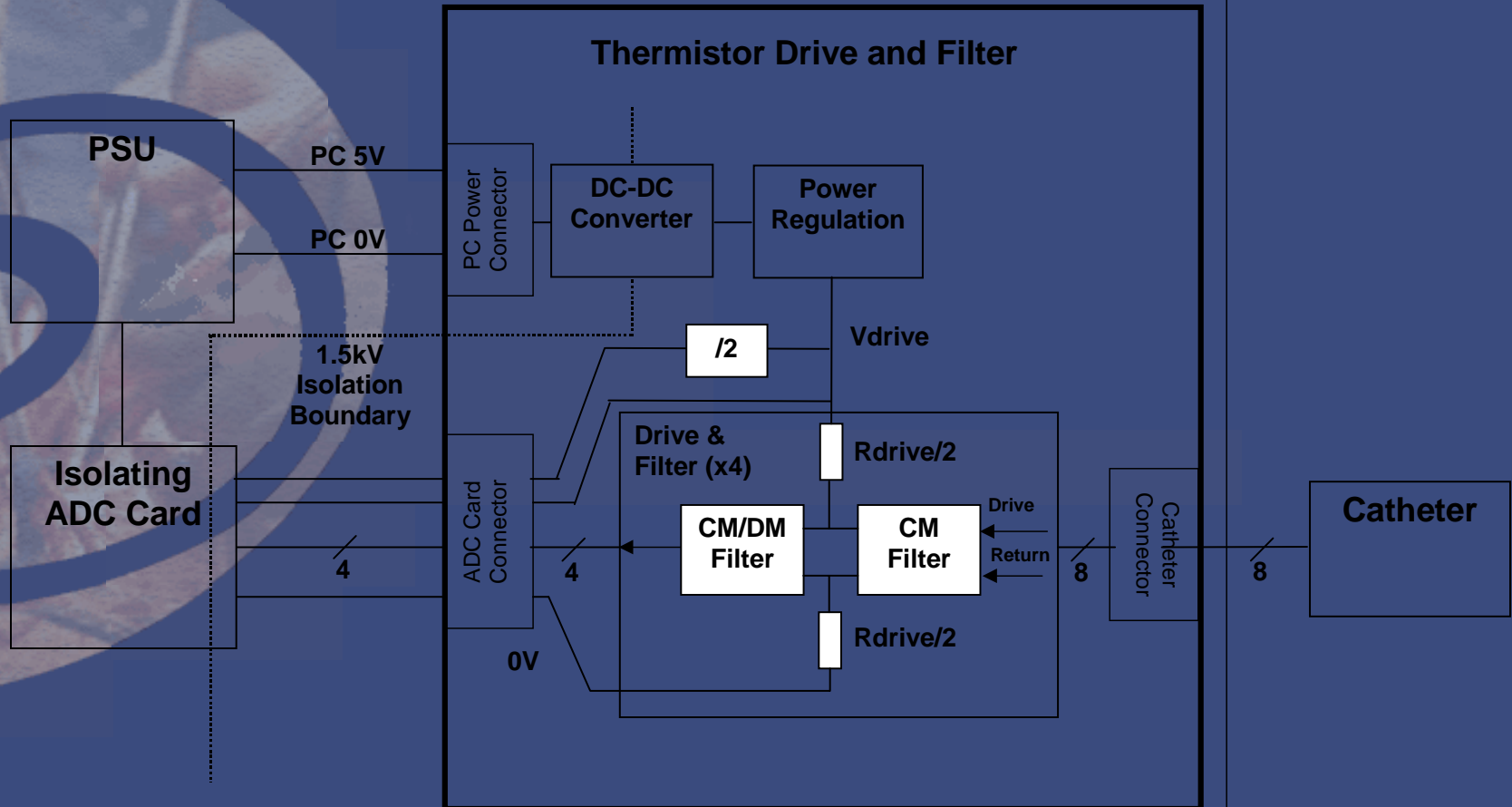
Patient safety isolation diagram



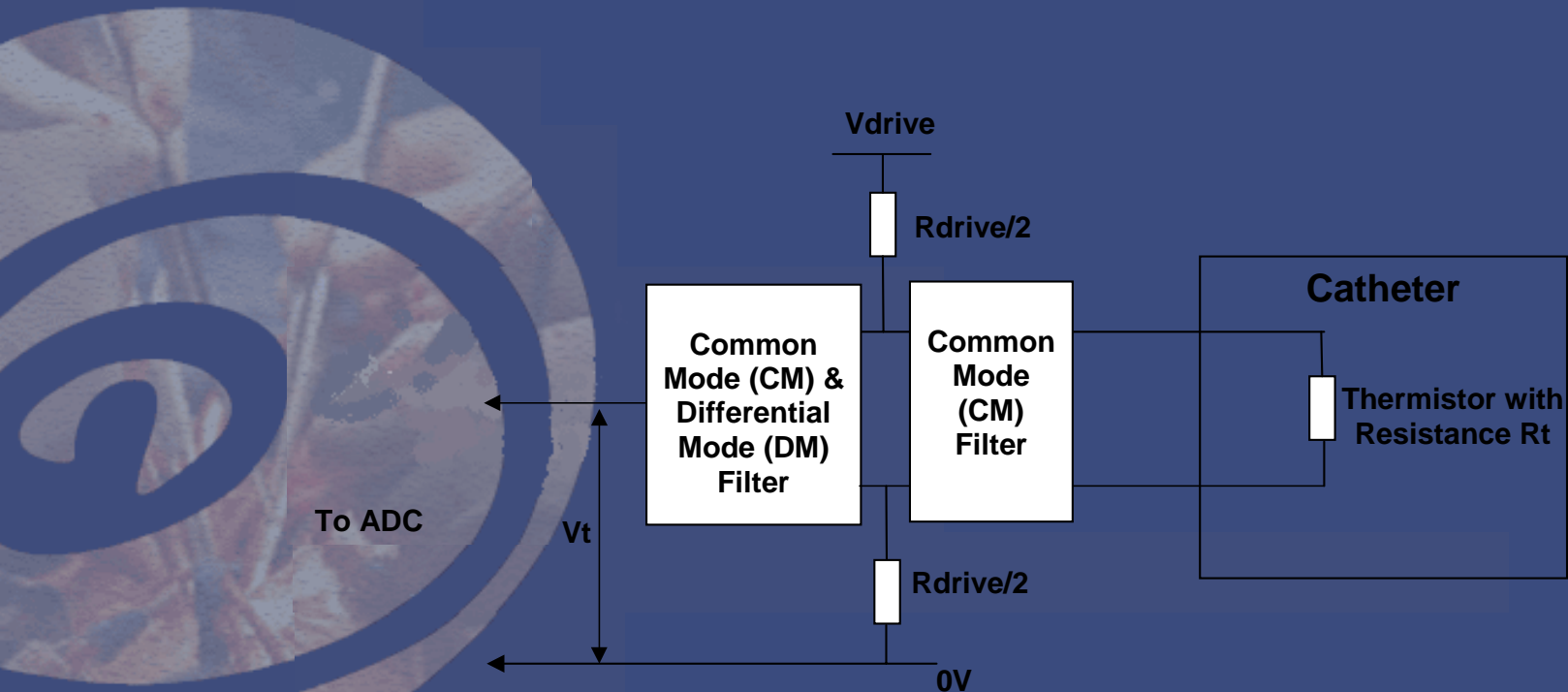
- 2500V isolation required
- Test to 1500V for Basic Isolation from Mains
- Test to 500V for Double isolation from Live Part

Thermistor Drive and Filter

Console



Apply voltage across drive resistor & thermistor half-bridge



Thermistor Resistance Sampling Strategy

Over-Sampling

- The ADC card selected is a 12-bit device. The input range set via software to 0-1.25V (the smallest available) which gives a resolution of $305\mu\text{V}$.
- The resolution required is 0.035% of the absolute resistance. The worst case is with the 5k7 device at 45 degrees C, since this has the smallest step size. Using the half bridge shown in with R_{drive} set to 8600 ohms, this corresponds to a change in voltage of $V_{\text{drive}} \times 6.65\text{e-}5$.

Thermistor Resistance Sampling Strategy

Over-Sampling

- The required resolution is therefore $81\mu\text{V}$, which can be met by over-sampling with the ADC. With a noise level of at least 1 LSB, over-sampling by a factor of N decreases the noise level by the square root of N .
- To get a minimum resolution of $81\mu\text{V}$ over-sampling must be by at least a factor of 15. This design shall over-sample by a factor of 40.

Software validation EN60601-1-4

System Risk assessment Estimated Risk

Software Risk Analysis

Requirements to control Risk

Risk Management Plan

Requirements Specification

Verification Validation Plan

Sub-system specification

Design Specification

PEMS architecture

Test Specification

Test Performance

Risk Management Summary.

Software validation EN60601-1-4

Verification testing

Level dependant on risk and classification MDD /FDA

Code reviews – Code walk through

Sub section testing – low level routines

Module testing – high level – user interface module

Verification testing scripts – functionality from Requirements spec

Integration testing – Testing scripts on complied code on actual hardware – full functionality

Validation testing – System performance testing – performed in target environment on final design hardware by users, in performance study.

Software validation EN60601-1-4

Source control – version control – bug/problem tracking

Important to maintain traceability of Requirements specification and Risk Analysis Requirements to defined tests at all / appropriate levels. Again dependant on Risk.

Verification & Validation tests vs Requirements Matrix

Off The Shelf Software – Operating System / Device Drivers / Software development tools – dependant on device risk.

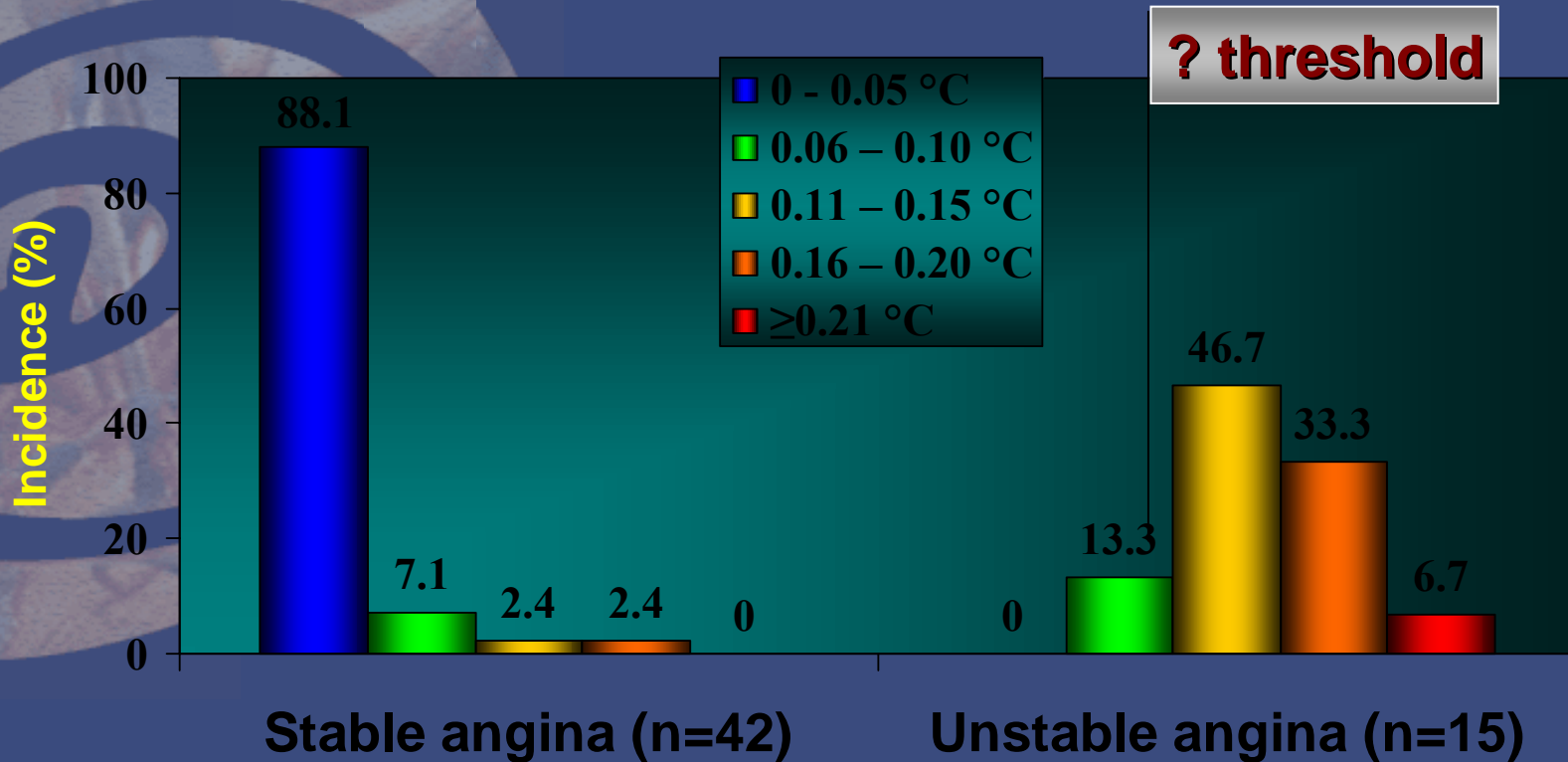


Where are we now?

Frequency of temperature elevation

- ◆ **CE Mark study** - all DS% <50%, **N=42**
- ◆ **Open use** - CAD, ACS, post MI, **N=15**

} **N=57**



Where are we going?



EU Clinical trial

+

US Clinical trial

**To develop the link between thermography
and cardiac events**