Apport de la TEP au FDG dans les infections cardiovasculaires

François Rouzet, MD, PhD

- Service de Médecine Nucléaire, GH Bichat-Claude Bernard, Paris, France
- LVTS (Inserm U1148), Team 4: cardiovascular imaging
- Université Paris Diderot, Sorbonne Paris Cité, France

Modified Duke criteria for the diagnosis of IE
(Adapted from Li & al)

MAJOR CRITERIA

Blood culture positive for IE

- Typical microorganisms consistent with IE from 2 separate blood cultures:
  Viridans streptococcus, Streptococcus bovis, HACEK group, Staphylococcus aureus or community acquired enterococci in the absence of a primry focus.

- Microorganisms consistent with IE from 2 persistely positive blood cultures:
  At least 2 positive blood cultures of blood samples drawn > 12 h apart or all of 3 or a majority of ≥ 4 separate cultures of blood with first & last sample drawn at least 1 h apart.

- Single positive blood culture for *Coxiela burneti* or phase I IgG antibody titer > 1:800.
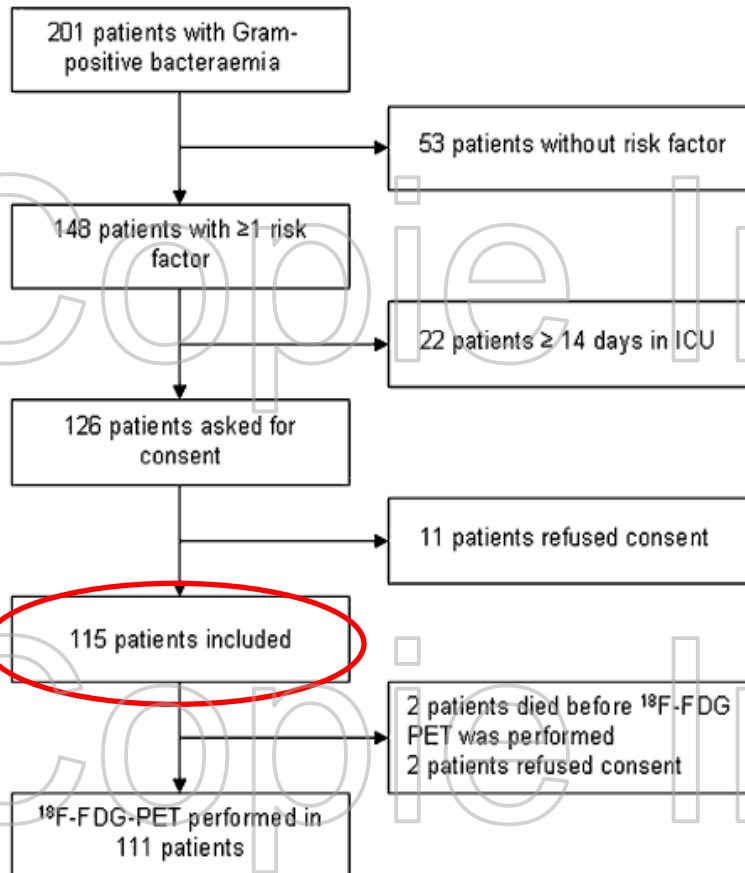
Evidence of endocardial involvement

- Echocardiogram positive for IE. *(Vegetation, Abscess, New partial dehiscence of prosthetic valve).*
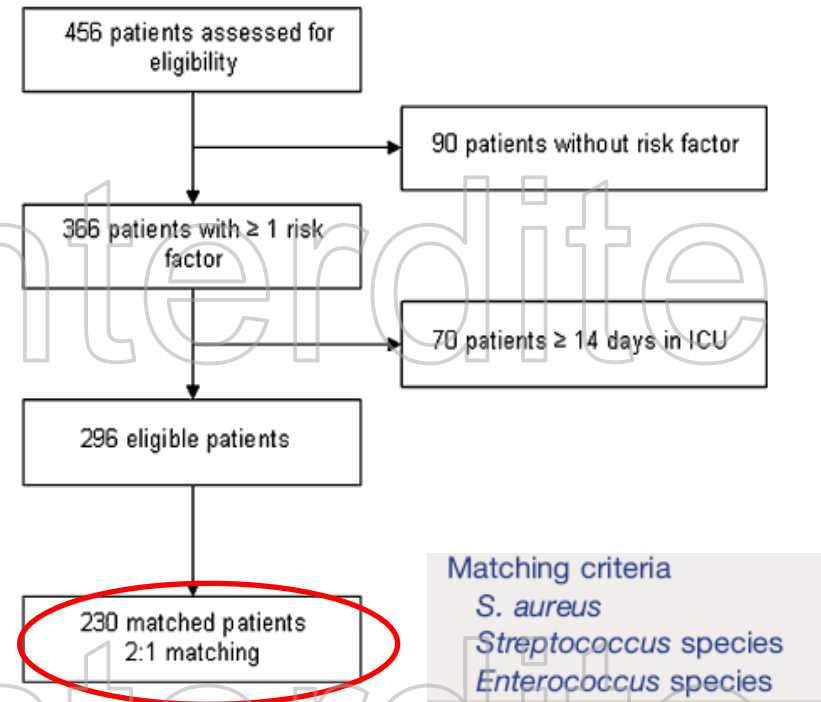- New valvular regurgitation.

MINOR CRITERIA

- Predisposition: Predisposing heart condition, injection drug use.
- Fever: temperature > 38°C.
- Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysms.
- Intracranial haemorrhages, conjunctival haemorrhages, Janeway lesions.
- Immunologic phenomena: glomerulonephritis Osler' s node, Roth' s spot, rheumatoid factor.
- Microbiological evidence: positive blood culture but does not meet a major criterion or serological evidence of active infection with organism consistent with IE.

^{18}FDG PET/CT for detection of metastatic infection in Gram-positive bacteraemia

Study patients

201 patients with Gram-positive bacteraemia

→ 53 patients without risk factor

148 patients with ≥1 risk factor

→ 22 patients ≥ 14 days in ICU

126 patients asked for consent

→ 11 patients refused consent

115 patients included

→ 2 patients died before ^{18}F-FDG PET was performed
2 patients refused consent

^{18}F-FDG-PET performed in 111 patients

Control patients

456 patients assessed for eligibility

→ 90 patients without risk factor

366 patients with ≥ 1 risk factor

→ 70 patients ≥ 14 days in ICU

296 eligible patients

230 matched patients 2:1 matching

Matching criteria
S. aureus
Streptococcus species
*Enterococcus* species

Vos FJ et al., J Nucl Med. 2010

TABLE 2. Localization of Metastatic Foci and Number of Foci First Detected by ^{18}F-FDG PET/CT

| Metastatic foci | Study patients (n = 115) | | | Controls (n = 230) | | P |
	Total number	%	First detected by ^{18}F-FDG PET	Total number	%	
Patients with foci identified	78	67.8		82	35.7	<0.01
Total number of foci	124			113		
Endocarditis	21	18.3	0	19	8.3	0.01
Endovascular	20	17.4	12	9	3.9	<0.01
Lung	12	10.4	6	8	3.5	0.01
Liver	1	0.9	0	1	0.4	1.0
Spleen	1	0.9	1	0	0	1.0
Arthritis	10	8.7	3	28	12.2	0.37
Spondylodiskitis	11	9.6	8	10	4.3	0.09
Osteomyelitis	6	5.2	1	3	1.3	0.06
Psoas abscess	3	2.6	2	1	0.4	0.11
Soft tissue	11	9.6	4	12	5.2	0.18
Central nervous system	11	9.6	3*	7	3.0	0.02
Eye	3	2.6	0	0*	0	0.04
Joint prosthesis	9	7.8	3	5	2.2	0.02
Intraabdominal	4	3.5	1	6	2.6	0.74
Kidney	1	0.9	0	4	1.7	0.67

*Epidural extension of ^{18}F-FDG uptake in 3 patients with spondylodiskitis, confirmed by MRI.
In 30 study patients and 22 controls, more than 1 metastatic localization was identified.

➢ **50% metastatic foci were asymptomatic**

Vos FJ et al., J Nucl Med. 2010
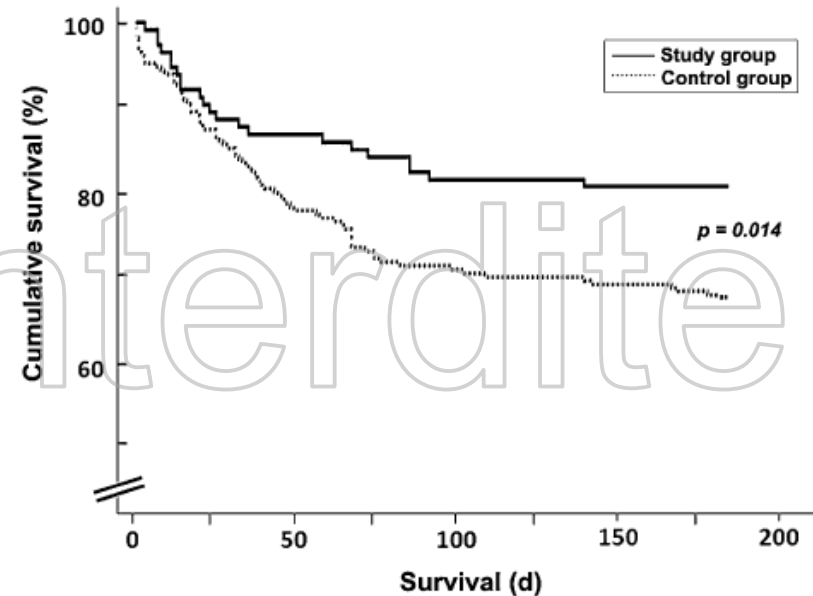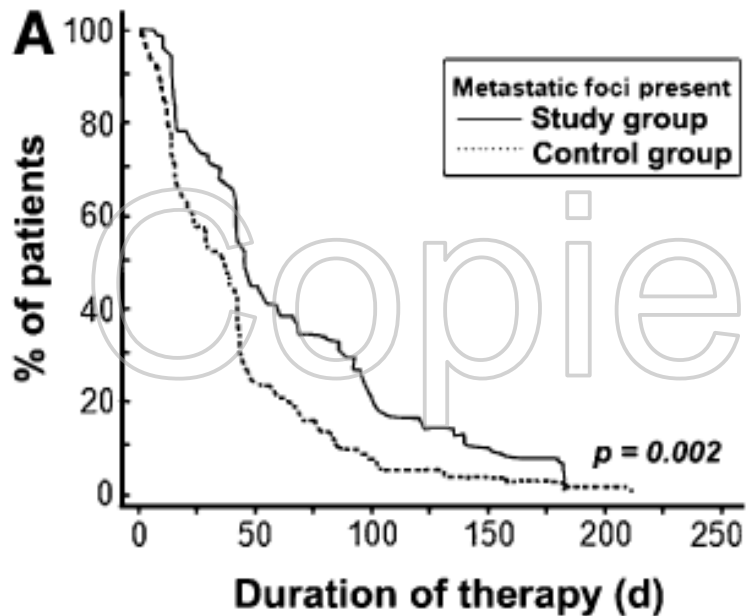
> **Relapse (3-month) : 2.6% *vs.* 7.4%**

> **_S. aureus_ subgroup : 1.4% vs. 8.9%**

Mortality (6-month) : 19% *vs.* 32%

Vos FJ et al., J Nucl Med. 2010

Infective endocarditis: embolic events

Patients:

- Single centre prospective study

- 71 patients (mean age: 55 y-o) *suspected* of IE

- HFLC beverage 45 min before FDG injection

- Valve: prosthetic (n=38); native (n=33)

Results:

- Unexpected extracardiac findings: 17 patients (24%)

- Antibiotic therapy at the time of PET/CT: 14/17

Bonfiglioli et al., Eur J Nucl Med. 2013

PET/CT positive for heart 1/neg. 0	Diagnosis confirmed by additional invest.	Not confirmed	Follow-up
0	Spondylodiscitis C7–D1		
0	Lung embolisms		
0	Spondylodiscitis L5–S1		
0	Lung embolisms		
0	Lung embolisms		
1	Splenic infarct and sternal osteomyelitis		Positive both at surgery and PET/CT, e.g. True Positive
1	Lung embolisms		
0	Spondylodiscitis L5–S1		
0	Lung embolisms		
1	Lung embolisms		
0	Lung embolisms		
0		Spondylodiscitis L5	
1	Spondylodiscitis L4–L5		
1	Spondylodiscitis L2–L3		Positive both at surgery and PET/CT, e.g. True Positive
0	Osteochondritis with an abscess		
0	Sternal osteomyelitis		

oncology-derived field of acquisition:
   skull base to upper thighs
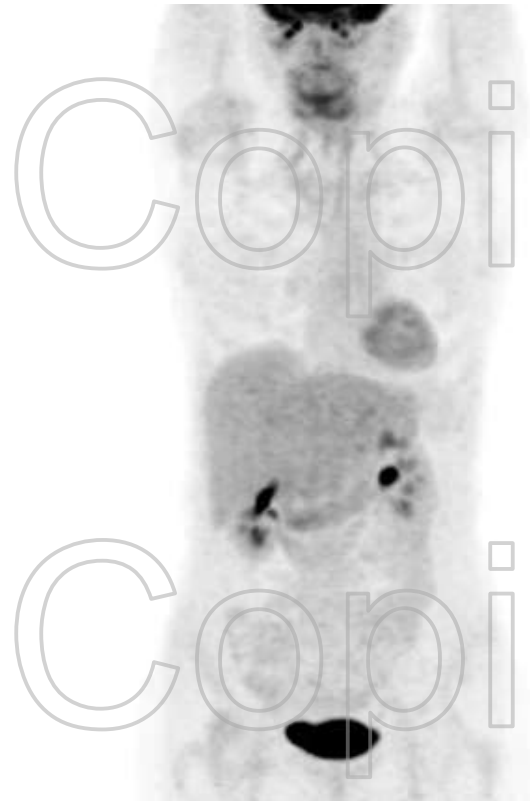
Trans Arterial Valve Implantation
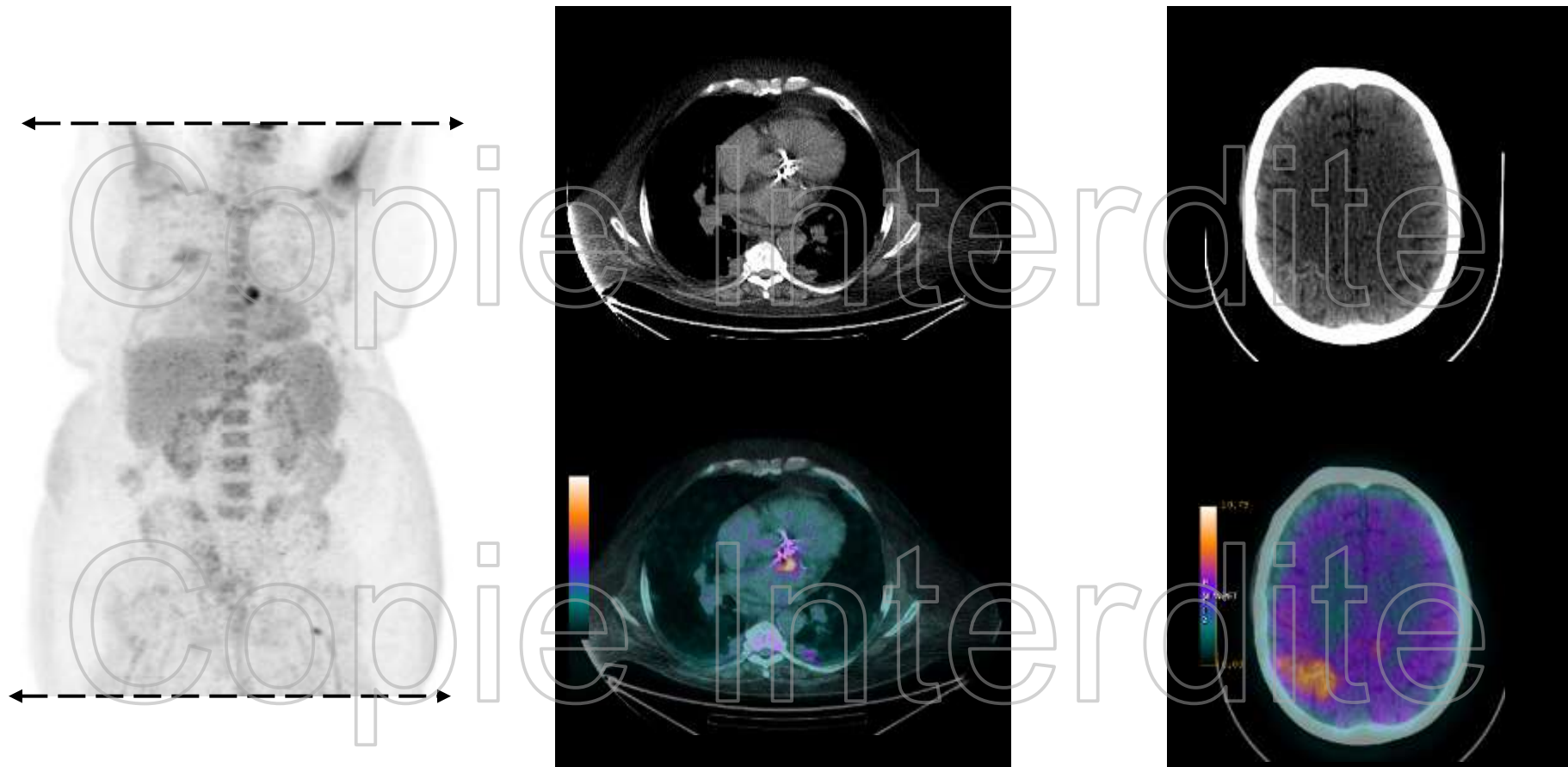
Detection of mycotic aneurysms of lower limbs by whole-body ^{18}FDG PET

Potentially severe complication of IE
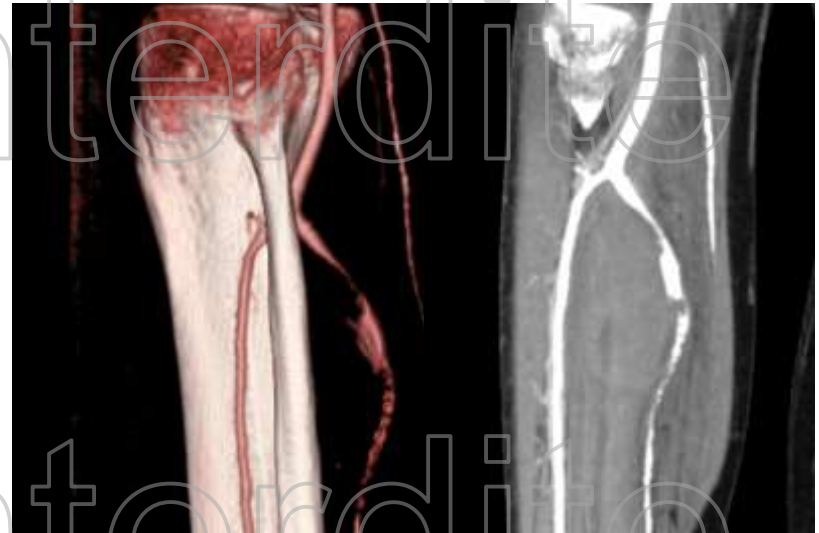
Incidence probably underestimated

PET/CT
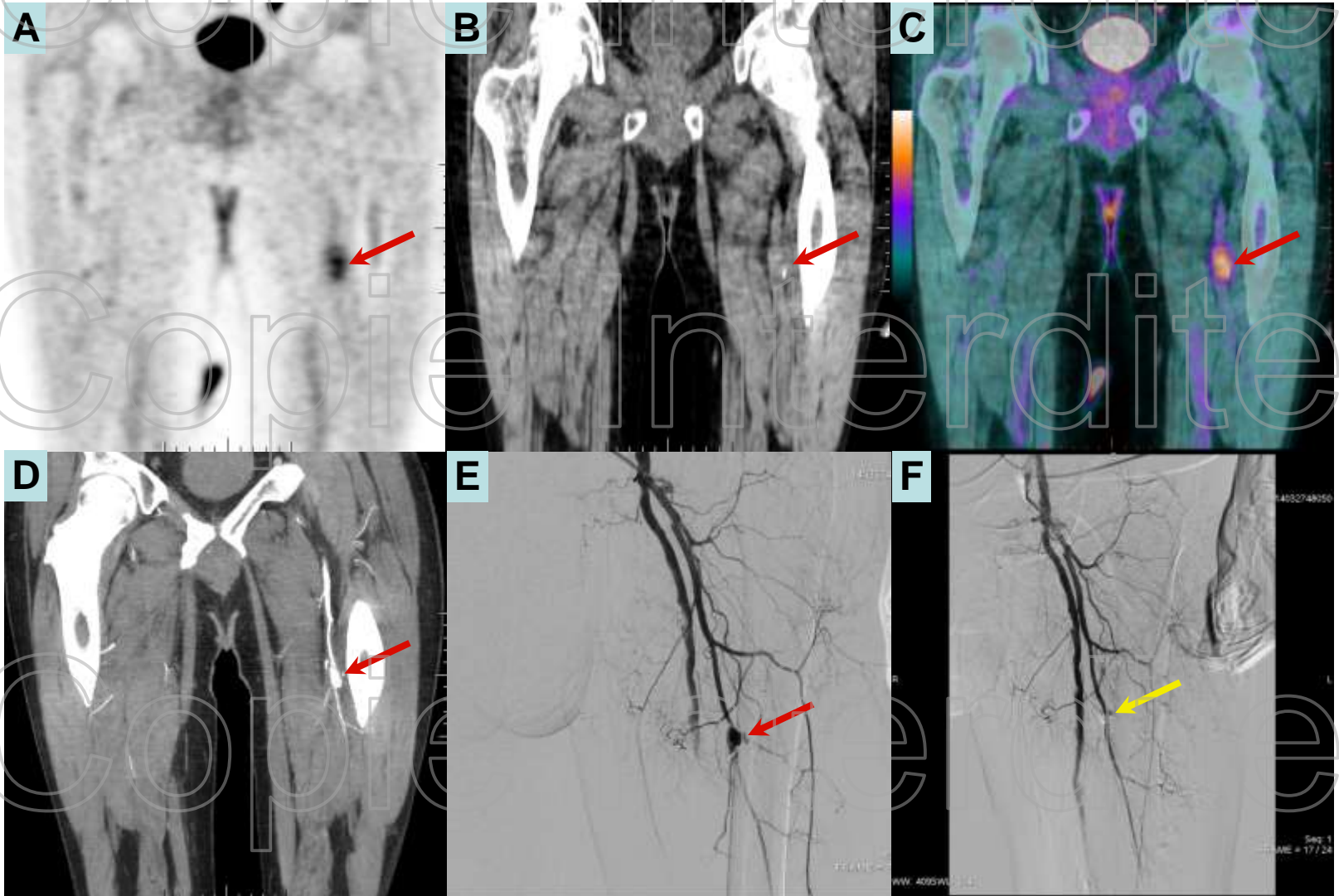
CT angio

Mikaïl N et al., JACC CV Imaging (in press)

Mycotic aneurysms

Mycotic aneurysms

- Recurrent finding of mycotic aneurysms of branches of femoral arteries, in relation with the extension of the field of acquisition of FDG PET/CT.

- Seems to be associated with haemorragic stroke

- Potential impact on IE management

- Recurrent chills, fever, and positive blood cultures (*E. faecalis*)
- Suspicion of aortic prosthetic valve infection
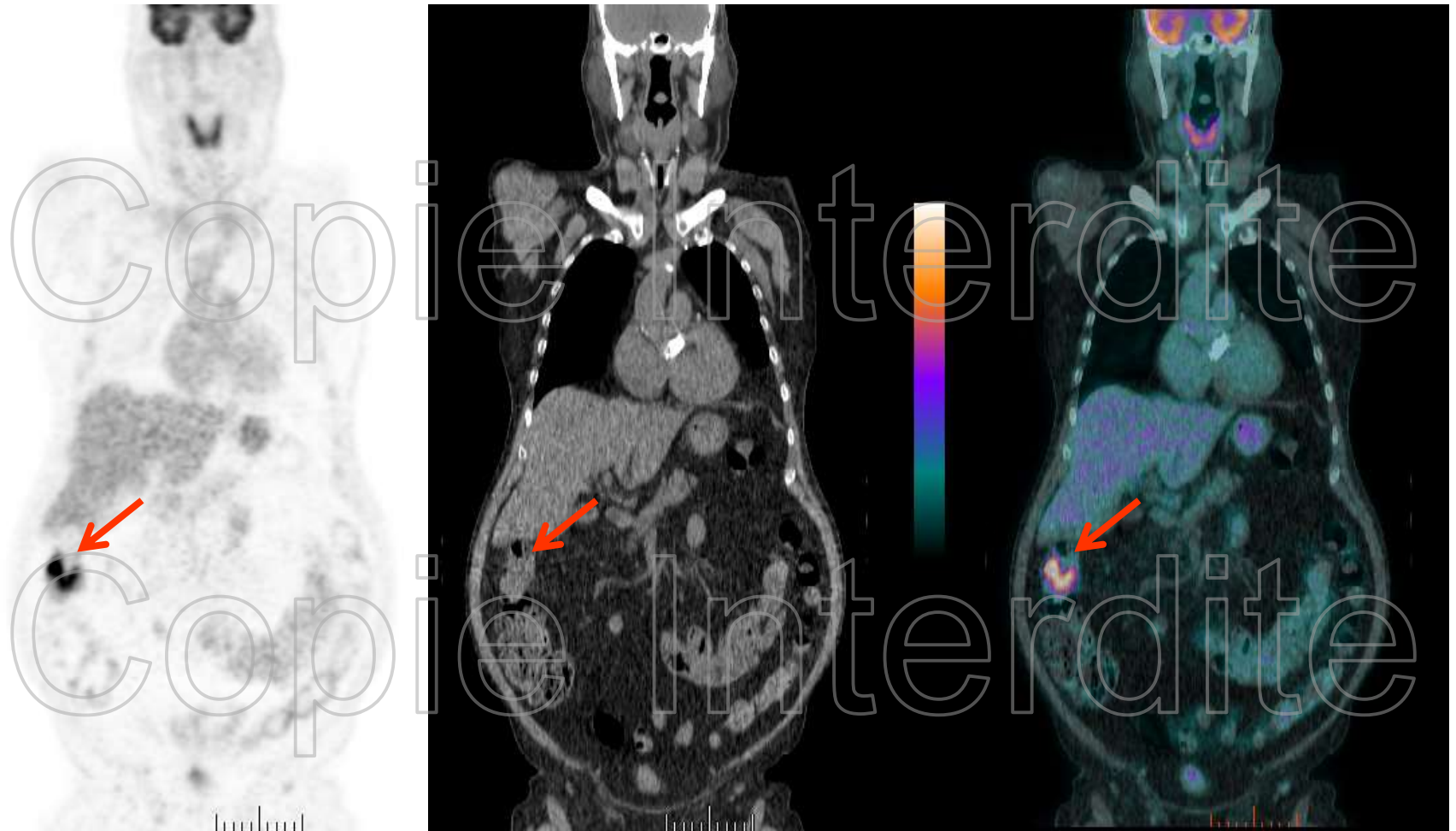
Valve (primary) lesion

Patients:

- Single centre prospective study (2005-2008)

- **No HFLC diet**

- 72 patients suspected of infective endocarditis

- 18 (25%) with definite IE (Duke criteria)

Results:

- Sensitivity: 39%; specificity: 93%; PPV: 64%; NPV: 82%

Outcomes	^{18}F-FDG uptake in or around the heart valves (%), $n=11$	No ^{18}F-FDG uptake in or around the heart valves (%), $n=61$	p value
Definite endocarditis according to the revised Duke criteria	7 (64)	11 (18)	<0.01
Prosthetic valve	1 (9)	1 (2)	0.01
Pacemaker lead infection	0 (0)	1 (2)	0.58
Relapse of infection	1 (9)	2 (3)	0.39
Mortality	4 (36)	11 (18)	0.22

Kouijzer et al., Eur J Nucl Med. 2013

– High Fat Low Carbohydrates (HFLC) diet
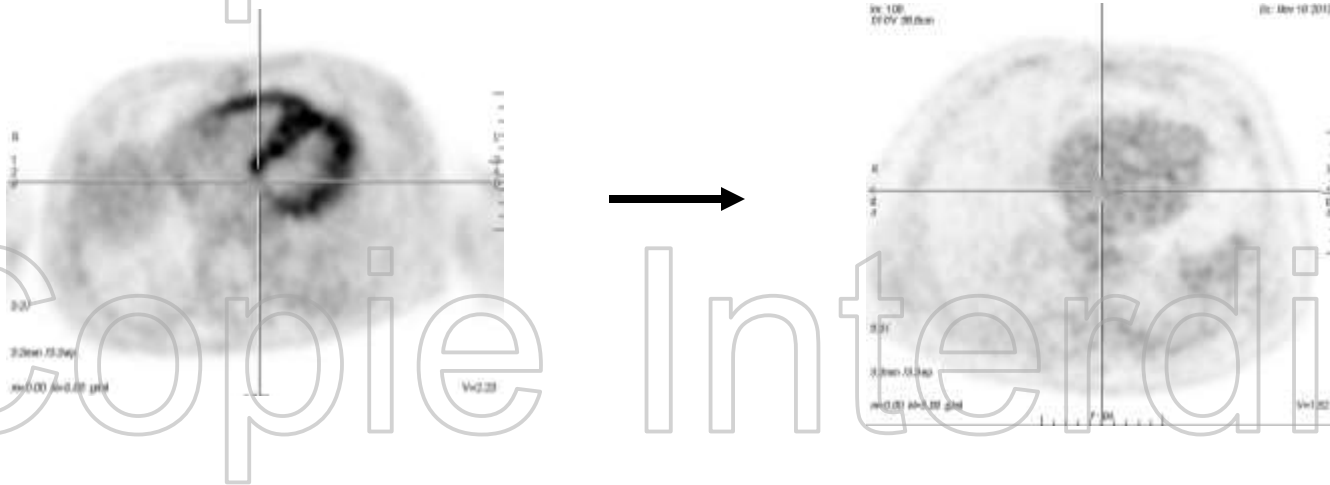
Insulin-dependent diabetes ?

- 12-hour fasting
- Blood glucose: 12.6 mM
- No myocardial uptake of FDG
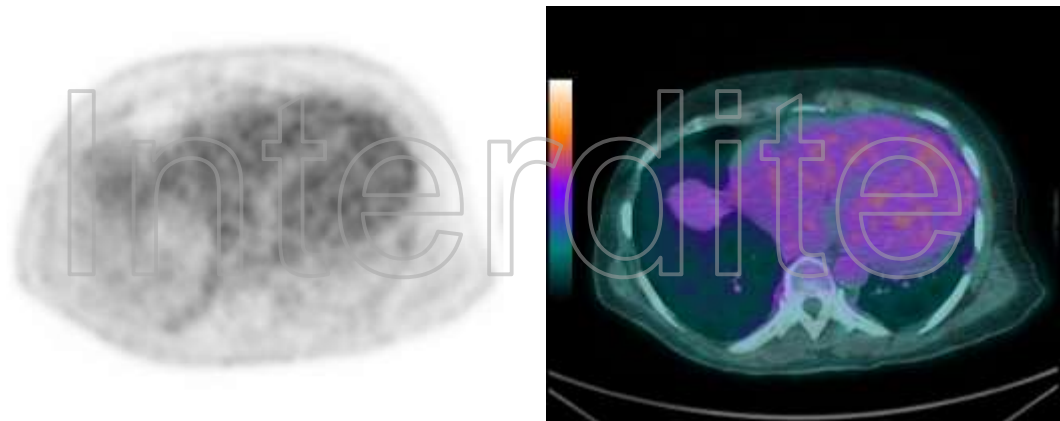
– Prosthetic valves: non attenuation-corrected images
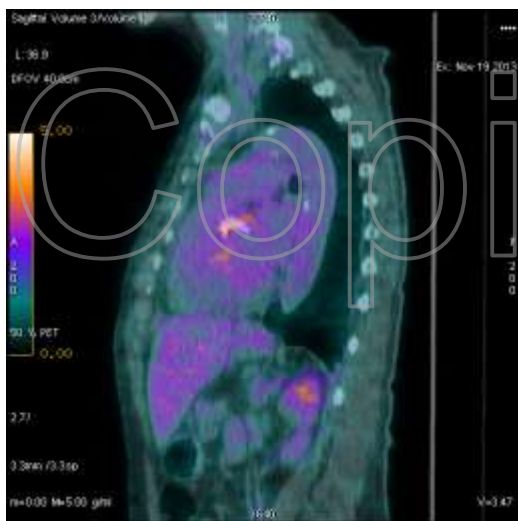
Attenuation
correction

No attenuation
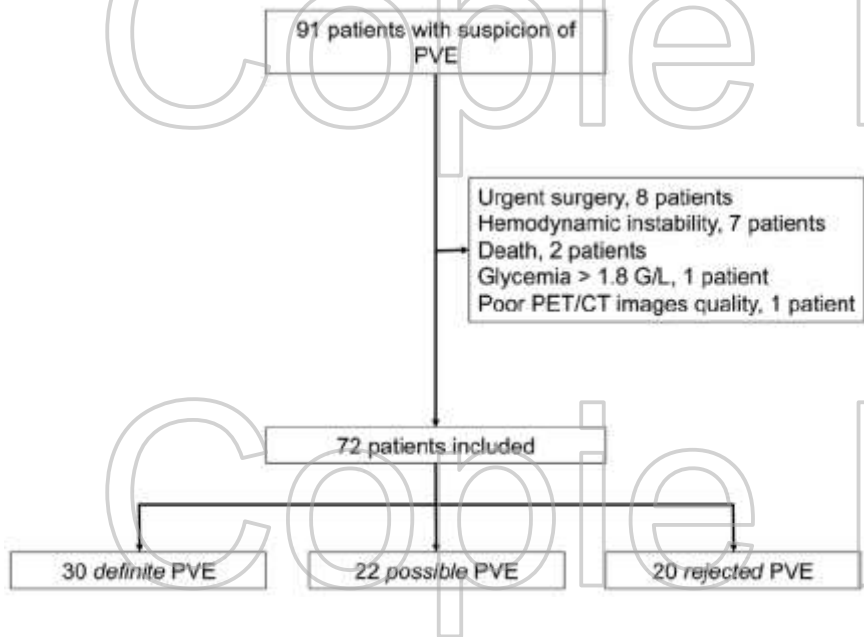correction

Prosthetic valve endocarditis (PVE)

91 patients with suspicion of PVE

Urgent surgery, 8 patients
Hemodynamic instability, 7 patients
Death, 2 patients
Glycemia > 1.8 G/L, 1 patient
Poor PET/CT images quality, 1 patient

72 patients included

30 definite PVE   22 possible PVE   20 rejected PVE

- − Delay >1 month after valve implantation (IQR: 526 to 3,396 days)

- − Median delay: 9 days (IQR: 5 to 19 days) after the beginning of antibiotherapy (n=55)

- − Positive PET/CT (n=36) in patients with biological and mechanical prosthetic valve: 52% vs. 46% (p=0.63)

| Table 3 | Results of PET/CT According to the Final Diagnosis |

	Final Diagnosis		
	Definite PVE	Possible PVE	Rejected PVE
Positive PET/CT	22 (73)	10 (45)	4 (20)
Negative PET/CT	8 (27)	12 (55)	16 (80)

Saby et al., JACC 2013

Prosthetic valve endocarditis

A p=0.02

SUVmax

B p=0.16

TBR
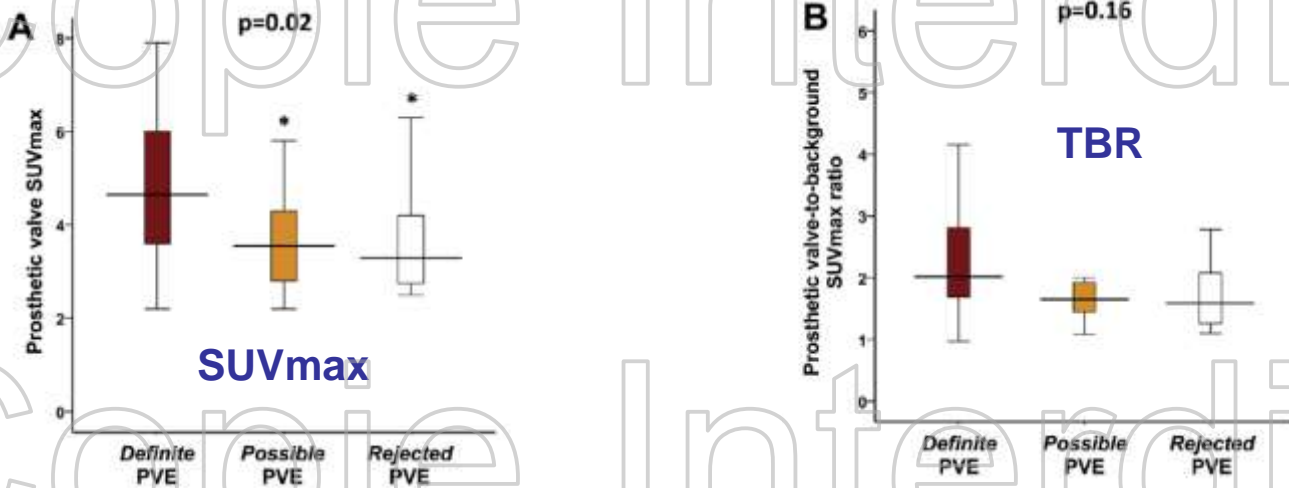
| Table 5 | Diagnostic Value of the Modified Duke Criteria at Admission With (Duke-PET/CT) and Without the Implementation of the PET/CT Results |

	Final Diagnosis		
	Definite PVE	**Possible PVE**	**Rejected PVE**
Duke			
Definite PVE	21 (70)	0 (0)	0 (0)
Possible PVE	8 (27)	22 (100)	10 (50)
Rejected PVE	1 (3)	0 (0)	10 (50)
Duke-PET/CT			
Definite PVE	29 (97)	10 (45)	2 (10)
Possible PVE	1 (3)	12 (55)	10 (50)
Rejected PVE	0	0	8 (40)

Saby et al., JACC 2013

Added Value of ^{99m}Tc-HMPAO–Labeled Leukocyte SPECT/CT in the Characterization and Management of Patients with Infectious Endocarditis

Erba PA et al, J Nucl Med 2012
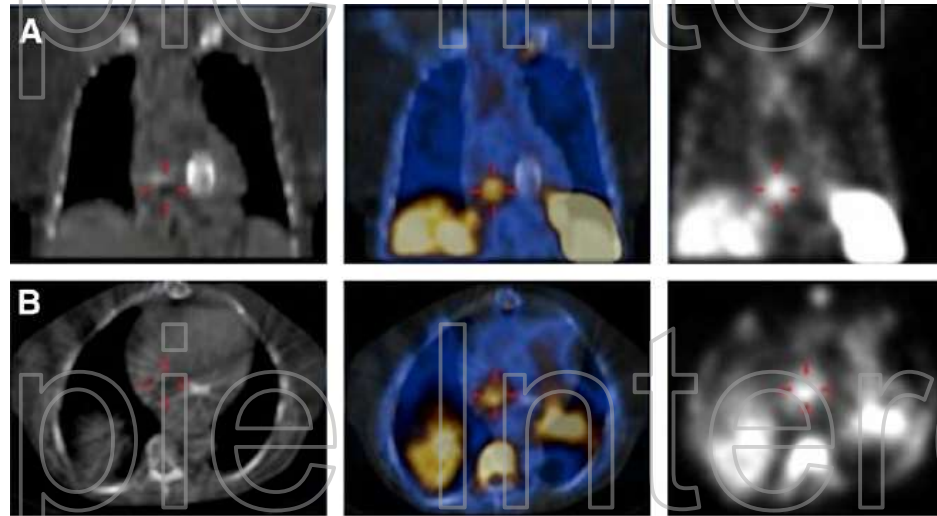
True-positive: 46 /51 ; False-negative: 5 /51 cases
(90% sensitivity, 94% NPV, and 100% specificity and PPV)

Results of ^{99m}Tc-HMPAO-WBC Scintigraphy in the 51 Patients with Final Diagnosis of IE, Stratified According to Duke Criteria

Duke criterion	Positive results			Negative results
	Cardiac only	Cardiac and extracardiac	Extracardiac only	
Definite IE (n = 24)	9	11*	0	4
Possible IE (n = 25)	13	11†	1*	0
Rejected IE (n = 2)	1	1*	0	0

FDG PET *vs.* WBC SPECT ?

- Single-centre prospective study (Bichat Hospital, Paris)

- 39 patients (males: 22), aged 62±17 years

- Suspected of prosthetic valve endocarditis (PVE)

- Delay between FDG PET and WBC SPECT: 7±7 days

- Diagnosis after ≥3-months follow-up (Duke-Li):

  – Definite, n=14 (36%)

  – Possible, n=3

  – Rejected, n=21

Rouzet F et al, J Nucl Med 2014

FDG PET *vs.* WBC SPECT ?

	Final diagnosis after ≥3 mo follow-up		
	Definite (n=14)	**Possible (n=4)**	**Rejected (n=21)**
FDG PET +	13 (93)	1	6
FDG PET -	1	2	15 (71)
WBC SPECT +	9 (64)	0	0
WBC SPECT -	5	3	22 (100)

- FDG PET false positive <2 months after valve implantation (n=6)

- WBC SPECT false negative (n=5): Coxiella (n=2), Candida (n=1), no abscess (n=2)

Detection of perivalvular regurgitation 40 days after valve replacement for PVE (*Nesseria sicca*)
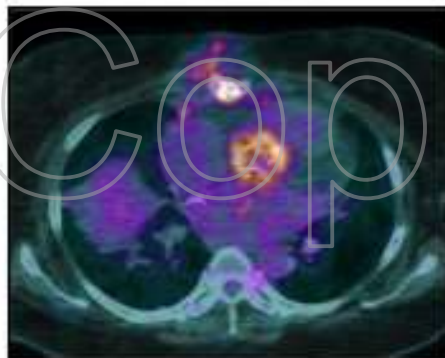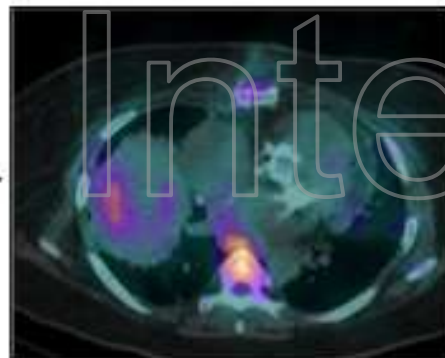

FDG-PET
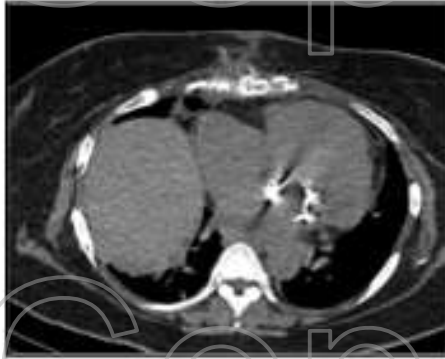
Leukocyte scintigraphy

CT

CT

PET
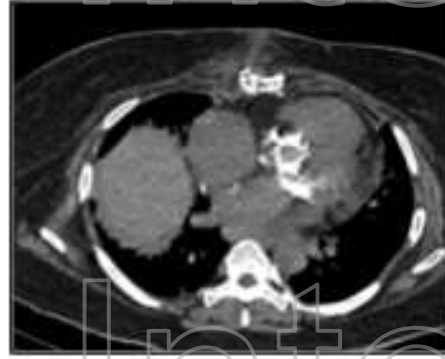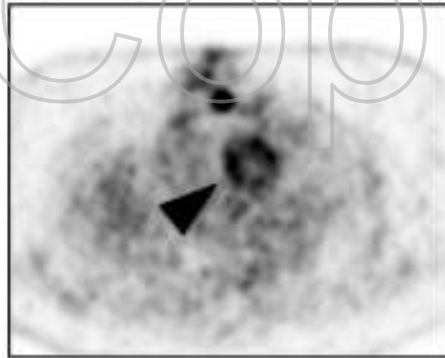
SPECT
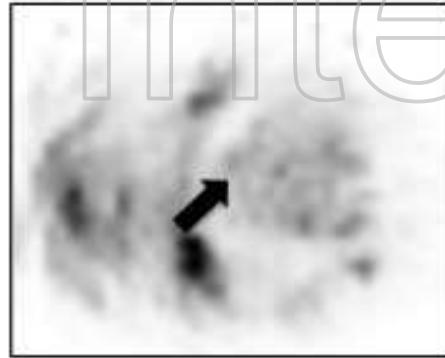
PET-CT

SPECT-CT

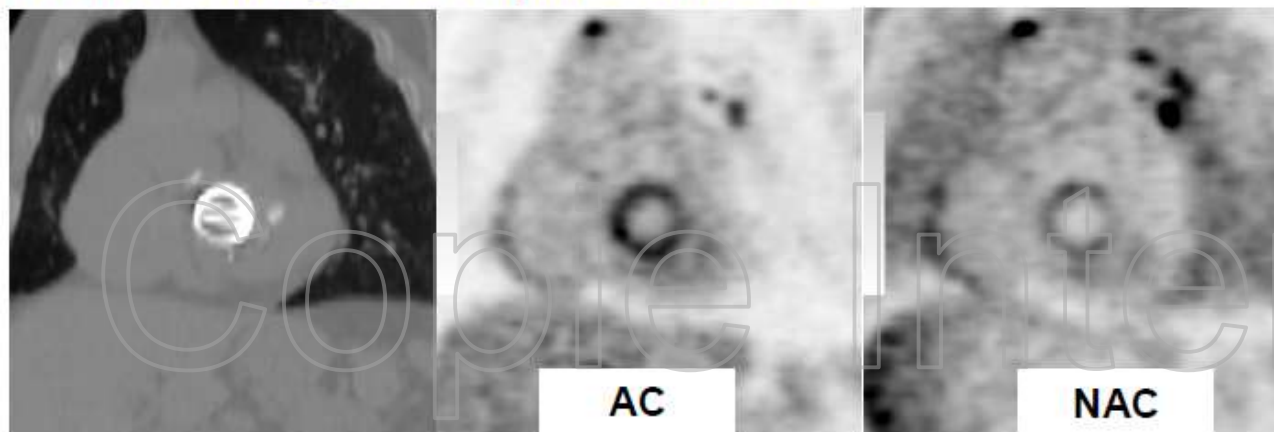- **No event during 6-months follow-up**

- **True negative WBC SPECT**

^{18}FDG uptake pattern in non-infected prosthetic heart valves

Absence of uptake on the PV

AC

NAC

Intense / Homogeneous uptake on the PV

AC

NAC

Mathieu C et al, SNM 2015

Modified Duke criteria for the diagnosis of IE
(Adapted from Li & al)

MAJOR CRITERIA

Blood culture positive for IE

- Typical microorganisms consistent with IE from 2 separate blood cultures:
  Viridans streptococcus, Streptococcus bovis, HACEK group, Staphylococcus aureus or community acquired enterococci in the absence of a primry focus.

- Microorganisms consistent with IE from 2 persistely positive blood cultures:
  At least 2 positive blood cultures of blood samples drawn > 12 h apart or all of 3 or a majority of ≥ 4 separate cultures of blood with first & last sample drawn at least 1 h apart.

- Single positive blood culture for *Coxiela burneti* or phase I IgG antibody titer > 1:800.
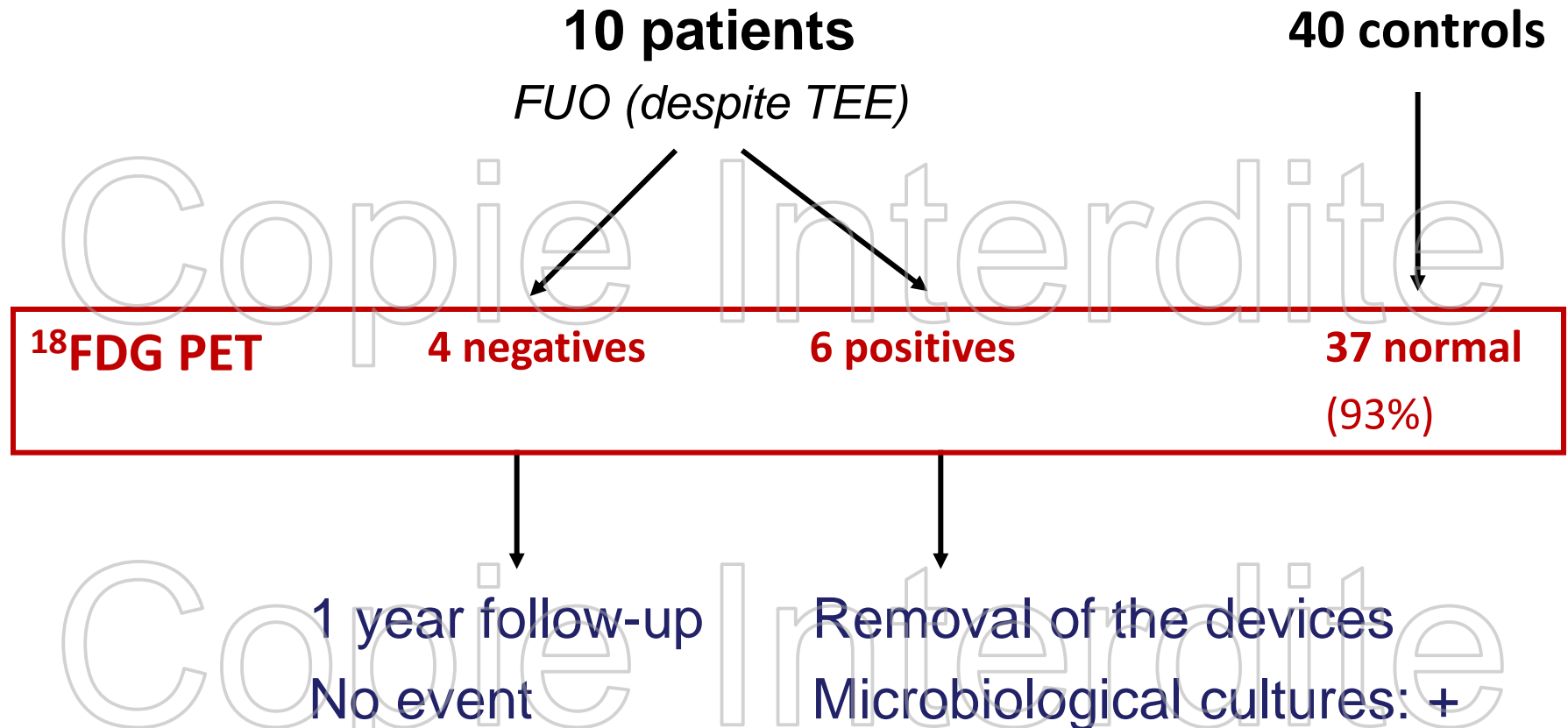
Evidence of endocardial involvement

- Echocardiogram positive for IE. *(Vegetation, Abscess, New partial dehiscence of prosthetic valve).*
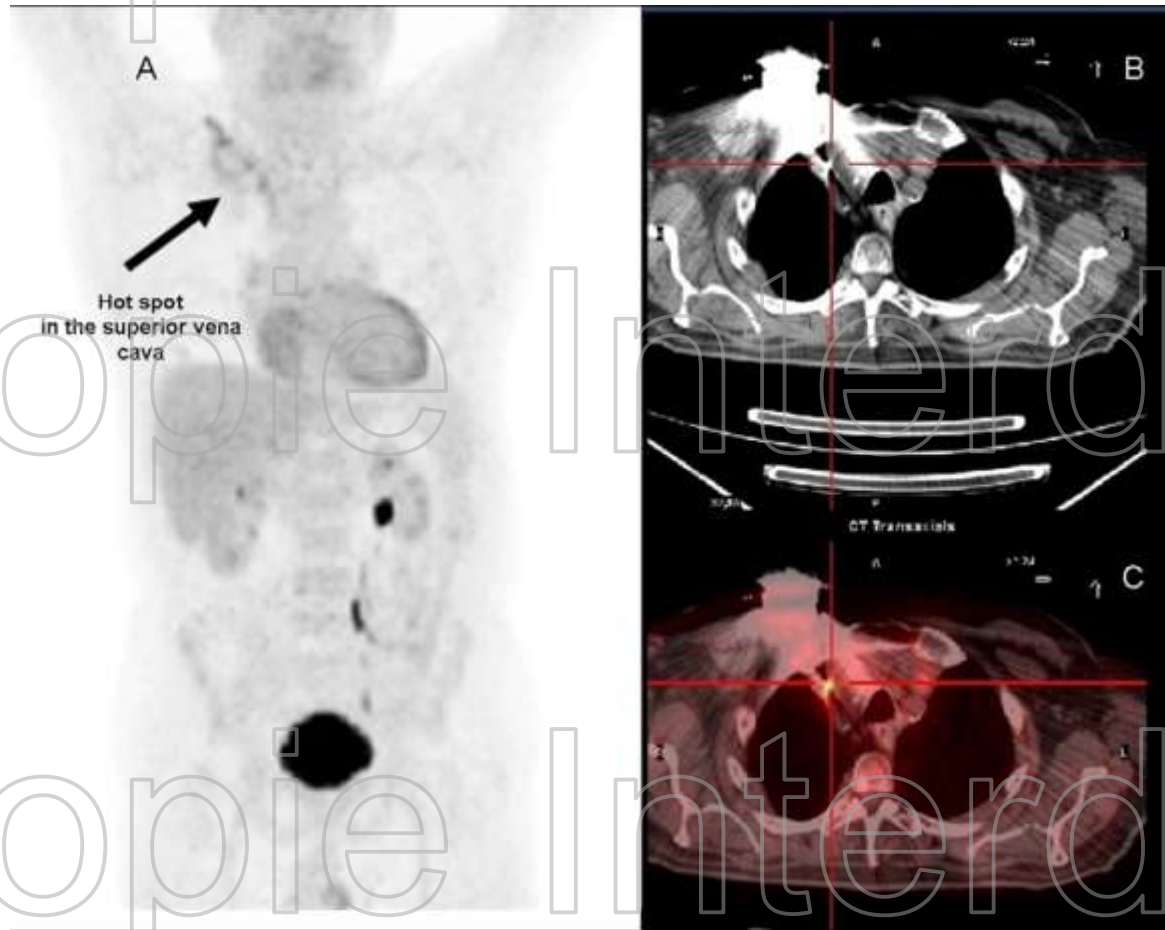- New valvular regurgitation.

MINOR CRITERIA

- Predisposition: Predisposing heart condition, injection drug use.
- Fever: temperature > 38°C.
- Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysms.
- Intracranial haemorrhages, conjunctival haemorrhages, Janeway lesions.
- Immunologic phenomena: glomerulonephritis Osler's node, Roth's spot, rheumatoid factor.
- Microbiological evidence: positive blood culture but does not meet a major criterion or serological evidence of active infection with organism consistent with IE.

CIEDs infection

10 patients

FUO (despite TEE)

40 controls

^{18}**FDG PET**   **4 negatives**   **6 positives**   **37 normal**
                                                                        (93%)

1 year follow-up   Removal of the devices
No event   Microbiological cultures: +

Ploux et al, Heart Rhythm 2011

Ploux et al, Heart Rhythm 2011

Usefulness of Fluorine-18 Positron Emission Tomography/Computed Tomography for Identification of Cardiovascular Implantable Electronic Device Infections

Sarrazin et al, J Am Coll Cardiol 2012

|	Group A Suspected CIED Infection (n = 42)	Group B Controls Acute Phase (n = 12)	Group C Controls Chronic Phase (n = 12)	p Value
Age, yrs	62 ± 17	65 ± 8	70 ± 10	0.189
Male/female, n	28/14	11/1	9/3	0.315
LVEF, %	44 ± 17	39 ± 13	50 ± 8	0.053
CAD	14 (33)	6 (50)	6 (50)	0.478
Diabetes mellitus	11 (26)	1 (8)	2 (17)	0.388
Warfarin	18 (43)	6 (50)	7 (58)	0.730
Corticosteroids use	3 (7)	0	0	1.000
Type of device				
Pacemaker	25 (60)	6 (50)	10 (83)	0.259
Defibrillator	17 (40)	6 (50)	2 (17)	
Biventricular device	7 (17)	3 (25)	0	0.781
Number of leads	2.2 ± 0.8	2.0 ± 0.7	1.8 ± 0.5	0.123
Time since last intervention, months	11.2 (0.3–101.5)	1.3 (1.0–2.1)	24.5 (8.0–130.2)	<0.001*
Confirmed infection	35 (83)	0	0	<0.001

PET - AC　　　**PET - NAC**

Group A

Group B

Group C
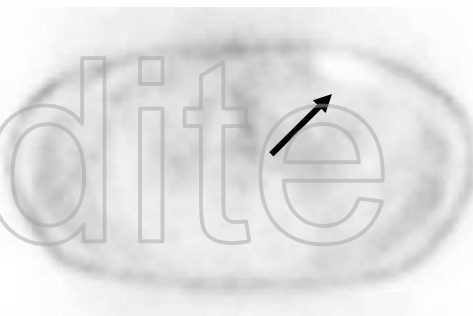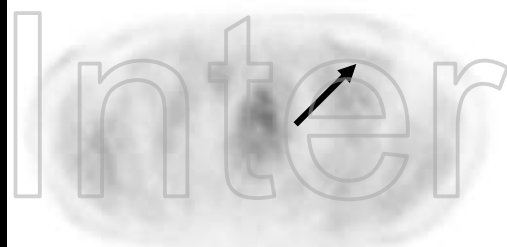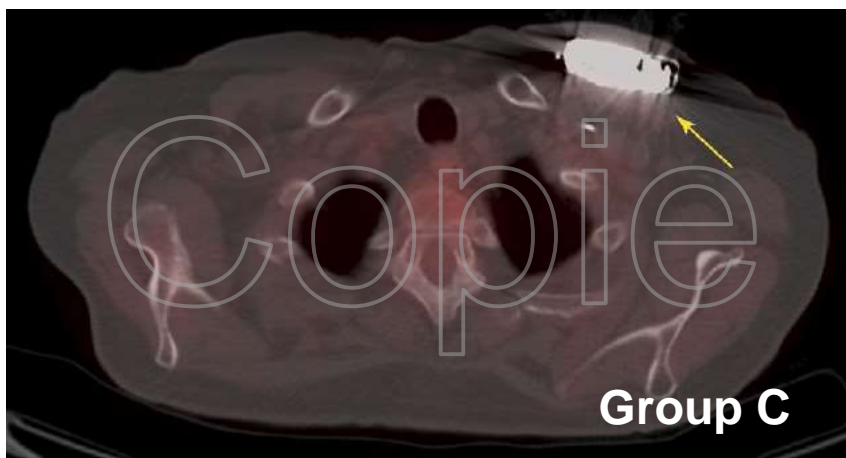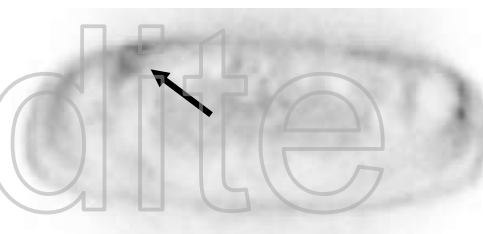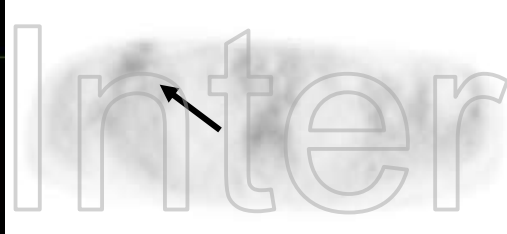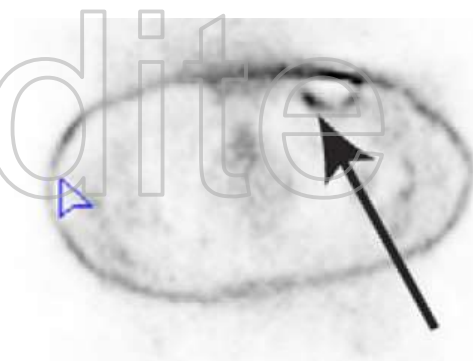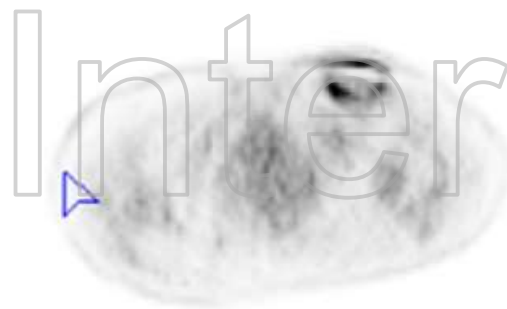
Delayed (3-hour) imaging

Leccisotti et al, J Nucl Cardiol 2014
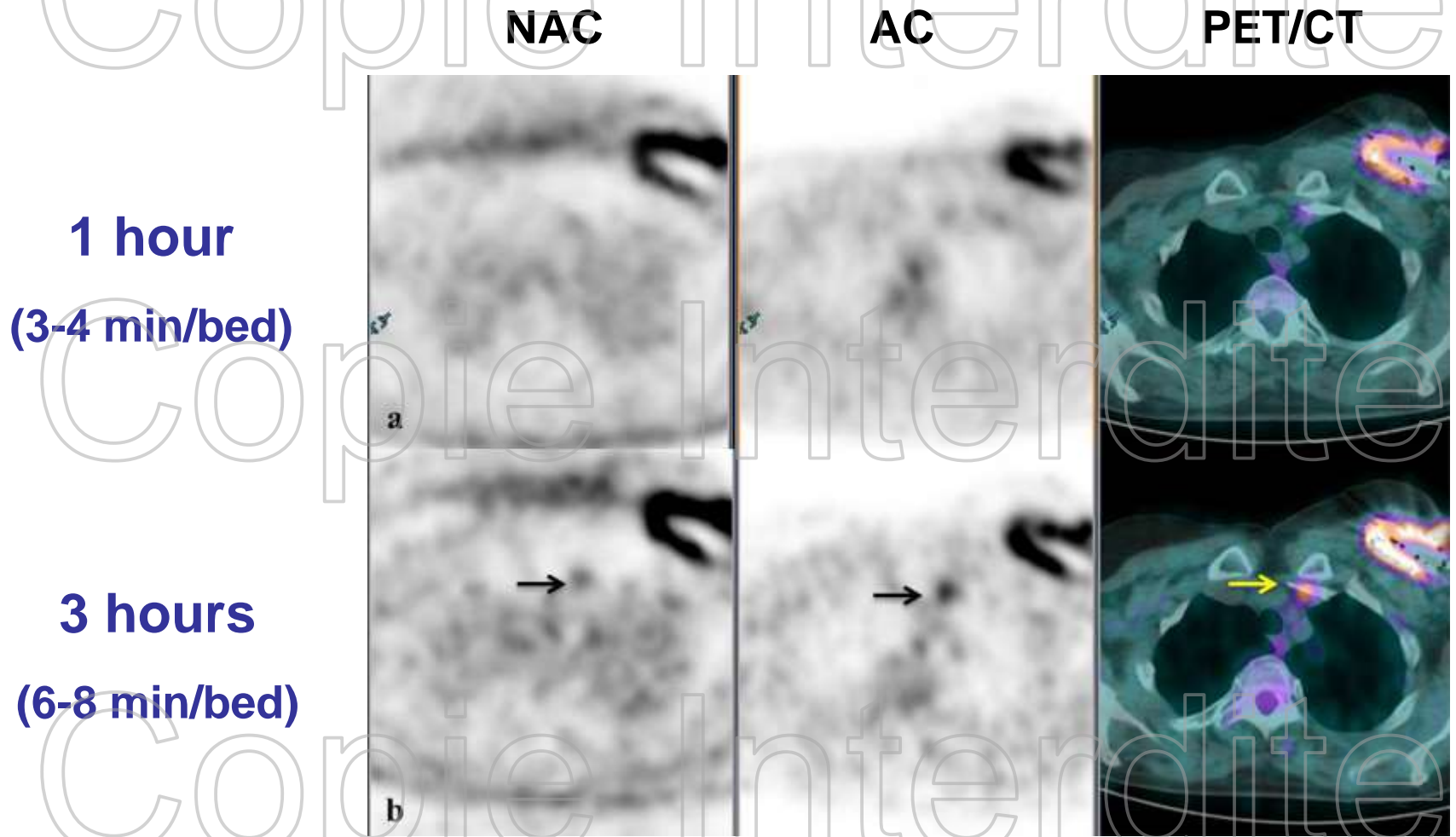
Table 3. Sensitivity, specificity, and diagnostic accuracy of standard (1-hour) and delayed (3-hour) FDG PET-CT imaging

	Standard FDG PET-CT	Delayed FDG PET-CT	P
Patient			
Sensitivity	86 (65–97)	91 (71–99)	ns
Specificity	100 (48–100)	100 (48–100)	ns
Accuracy	93 (76–99)	95 (80–99)	.7
Pocket			
Sensitivity	89 (65–98)	94 (73–99)	ns
Specificity	100 (66–100)	100 (66–100)	ns
Accuracy	94 (78–99)	97 (82–99)	.59
Leads	*(n=6)*	*(n=11)*	
Sensitivity	24 (5–54)	61 (32–86)	ns
Specificity	79 (49–95)	79 (49–95)	ns
Accuracy	51 (31–70)	70 (49–86)	**.024**

Bold value is statistically significant
Data are expressed as percentage (95% confidence interval)
FDG, ^{18}F-fluorodeoxyglucose; ns, not significant; PET-CT, positron emission tomography-computed tomography

Leccisotti et al, J Nucl Cardiol 2014

Summary

WBC scintigraphy
- Well established in infection
- Specificity +++

FDG PET in infective endocarditis
- Allows early identification of
  - Septic emboli / metastatic infection
  - Portal of entry
- Impacts on diagnosis of PVE
- Impacts on patients' management

Flowcharts
- Saby L. et al., JACC 2013
- Iung B. et al., Q J Nucl Med Mol Imaging 2014
- ESC/EANM guidelines on infective endocarditis (Hamburg 2015)

Remains to be determined
- Cost-effectiveness
- Diagnostic value, impact on patients' management and outcomes in multicentre trials

- **NCT01916005** - *F. Thuny, Marseille, France*

Diagnostic Value of 18F-fluorodeoxyglucose Positron Emission Tomography/Computed Tomography in Prosthetic Valve Endocarditis.

- **TEPvENDO** - *X. Duval, Bichat, Paris, France*

Diagnostic and therapeutic impact of FDG PET at the acute phase of infective endocarditis (8 centres).

- **ENDOTEP** - *P. Bordachar, Bordeaux, France.*

Assessment of the diagnostic accuracy of FDG PET in the diagnosis of cardiac devices infection: a prospective multicentre study.
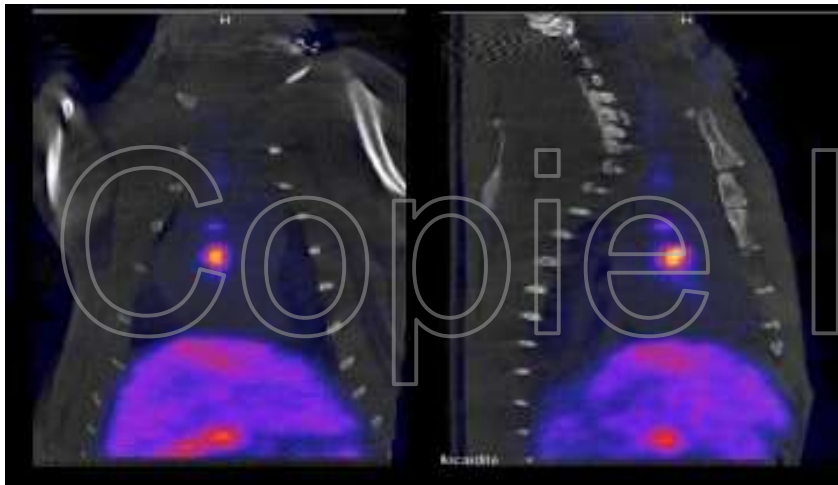
Perspectives: new imaging agents

Leukocytes labelled with positron emitters (PET)

- Requires a long half-life isotope (^{64}Copper = 12.7 hours)
- *Bhargava et al. NMB 2009*

^{99m}Tc-Annexin A5

- Target: vegetations (phosphatidylserine expressed by activated platelets)
- No physiological uptake in heart and brain

AnnIE
Sponsor: Inserm
Proof-of-concept study
Patients suspected of IE
Kick off: 2015

Rouzet et al., Circulation 2008
Benali et al., Mol Imaging 2014