CML and Tyrosine Kinase Inhibitors – What are the Cardiovascular Toxicities? Should Everyone Get an Ankle Brachial Index (ABI) Before Starting?

Joerg Herrmann, M.D.

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DISCLOSURE

Relevant Financial Relationship(s)

ARIAD Pharmaceuticals, Advisory Board

Bristol-Myers-Squibb, Advisory Board

Amgen, Advisory Board

Off Label Usage

None

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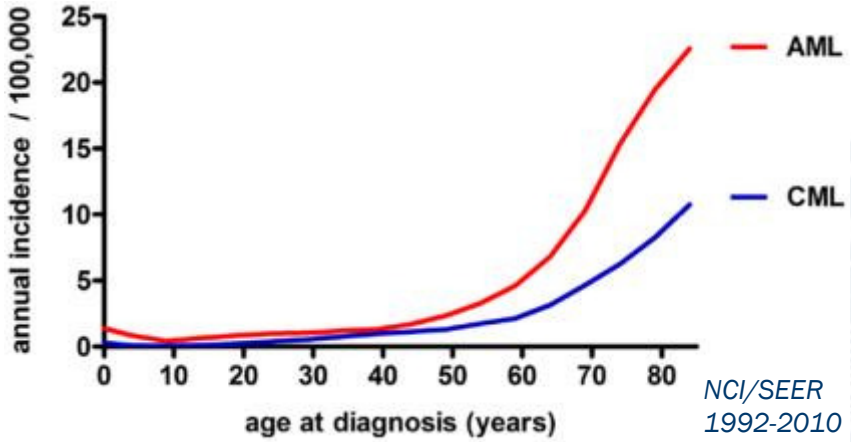
CML Facts

- CML accounts for approx. 15-20% of adult leukemias

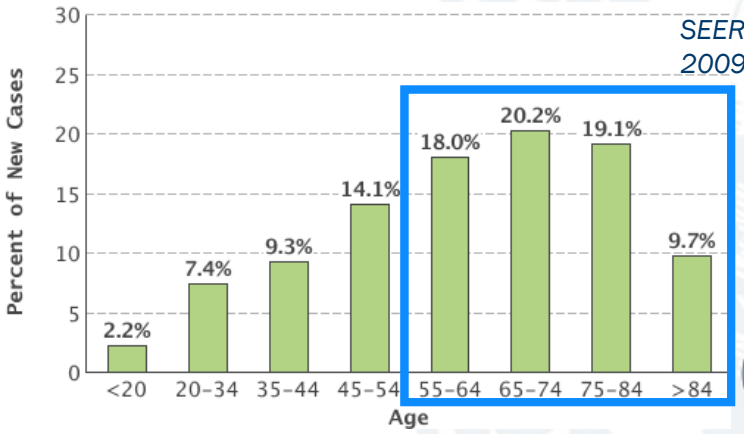
- annual incidence of 1 to 2 cases per 100,000

- median age at presentation 64 years

- 2/3 are 55 and older



NCI/SEER 1992-2010



SEER 2009-2013

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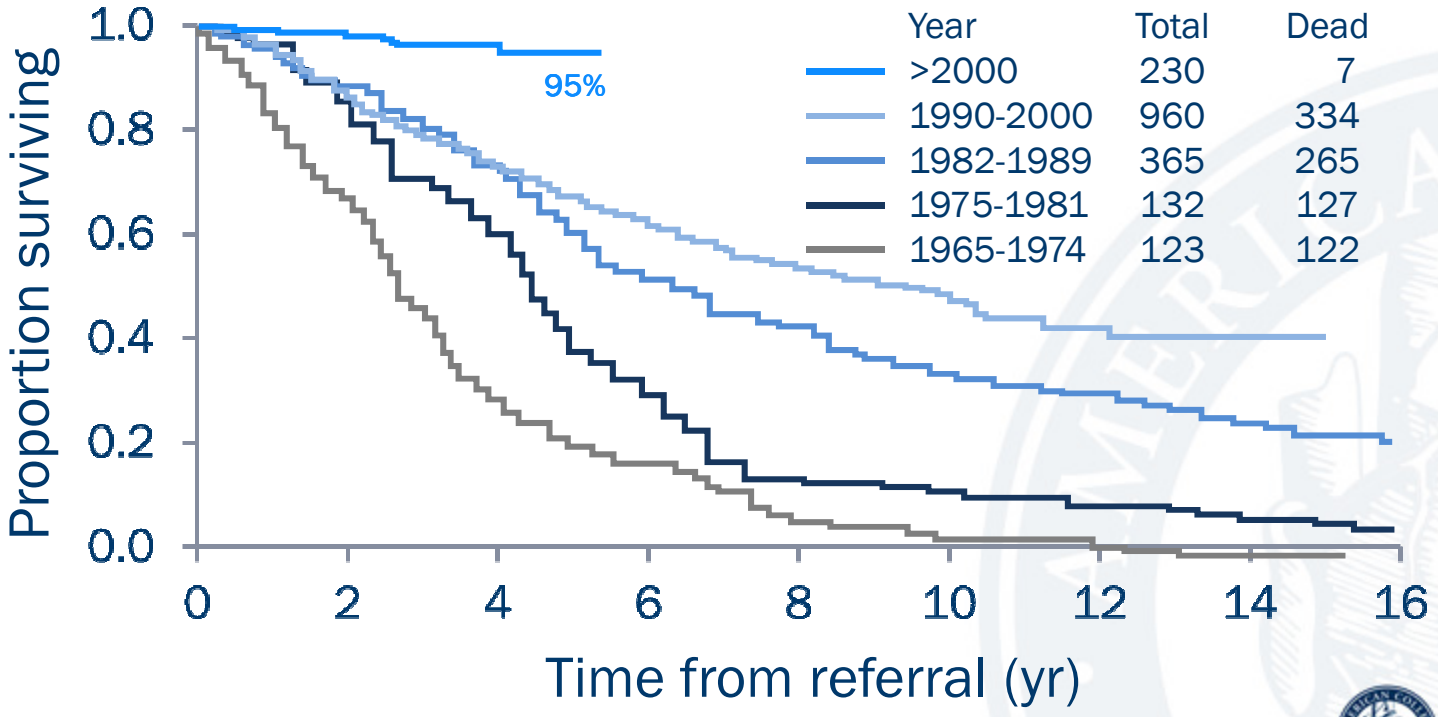
CML Prognosis

Survival Improvement Over Time



Quintas-Cardama A, Cortes JE: Mayo Clinic Proc 81:973, 2006

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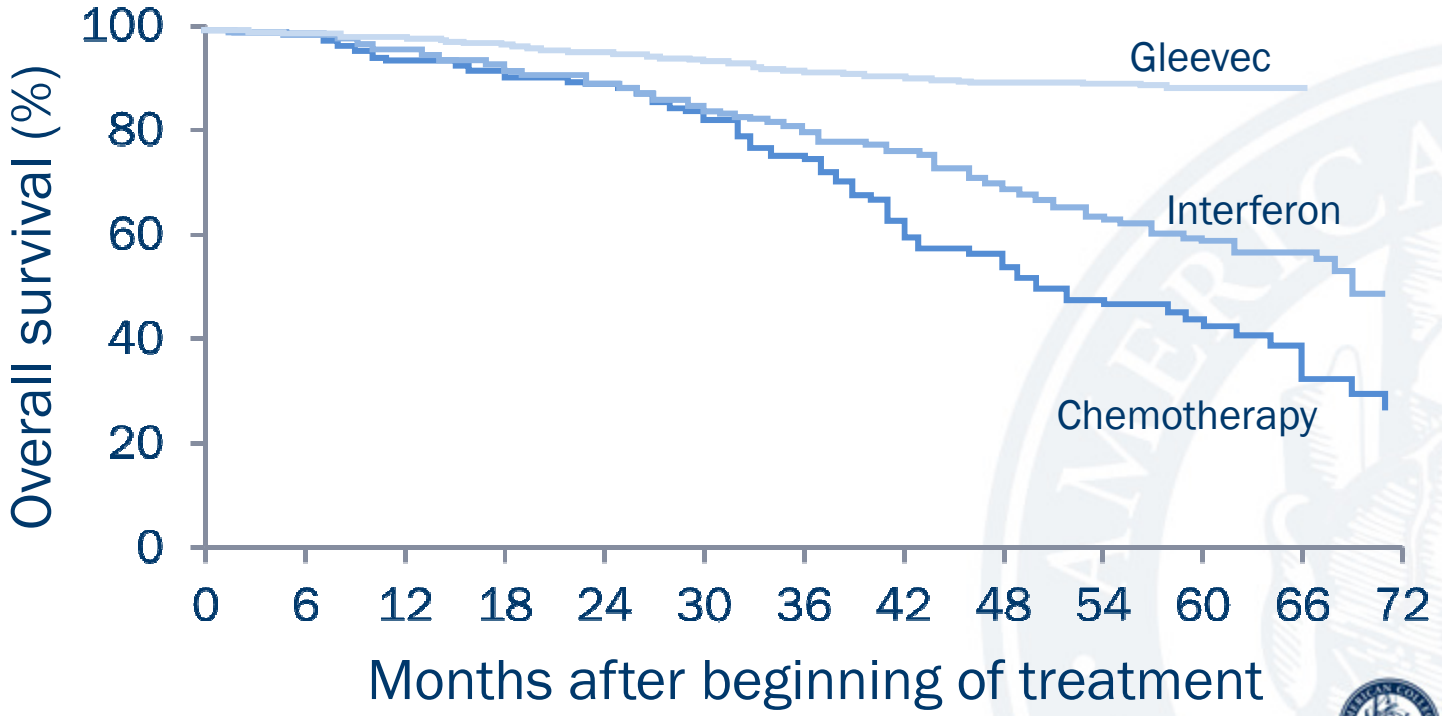
CML Survival Improvement

Success of Advances in Chemotherapies



Druker BJ et al: NEJM355:2408, 2006
Italian Cooperative Study Group: NEJM 330:820, 1994

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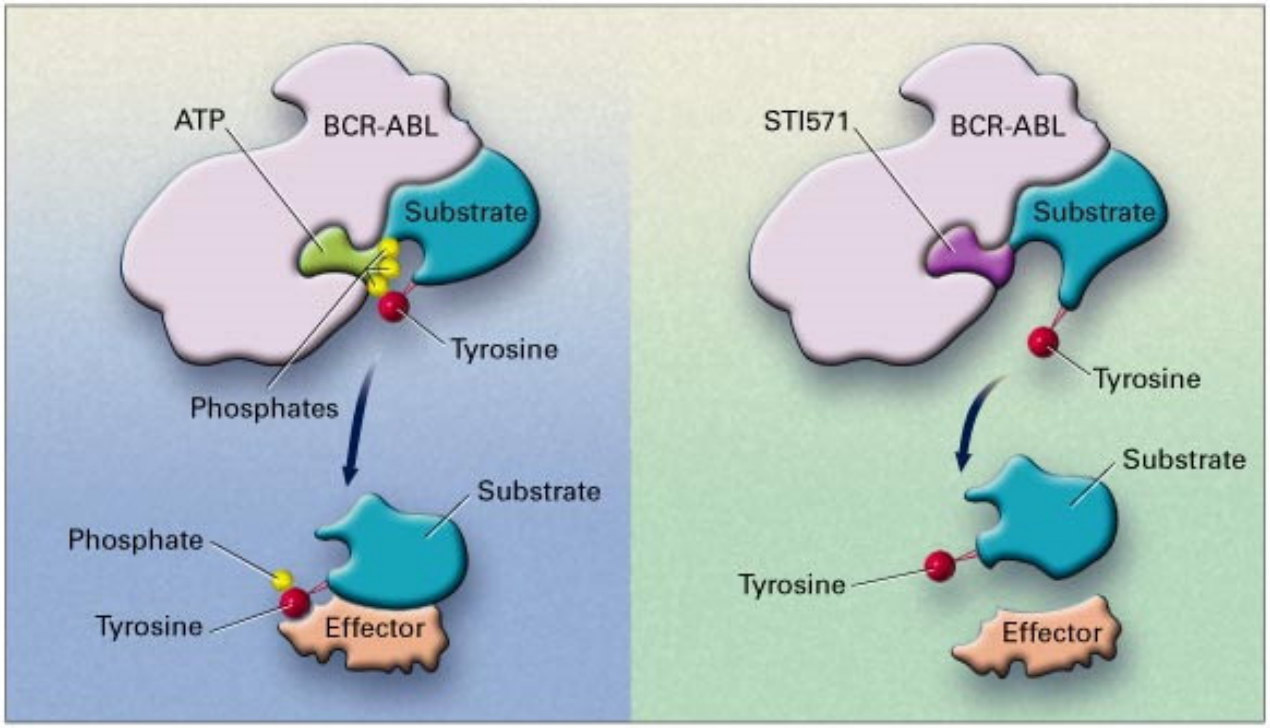
Bcr-Abl TKIs

The Epitome of the Success of Targeted Therapies



Same venue for

Ph+
Acute
Lymphoblastic
Leukemia

Faderl S et al. N Engl J Med 1999;341:164-72
Goldman JM, Melo JV. N Engl J Med 2001;344:1084-6

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Success of Bcr-Abl-directed Therapies

CML as a Chronic, Non-Fatal Disease

"Ashes to ashes, dust to dust,
if the cancer don't get us,
the arteriosclerosis must"

Richard Gordon
in The Alarming History of Medicine, 1993

Druker BJ et al. N Engl J Med. 2006;355:2408-17

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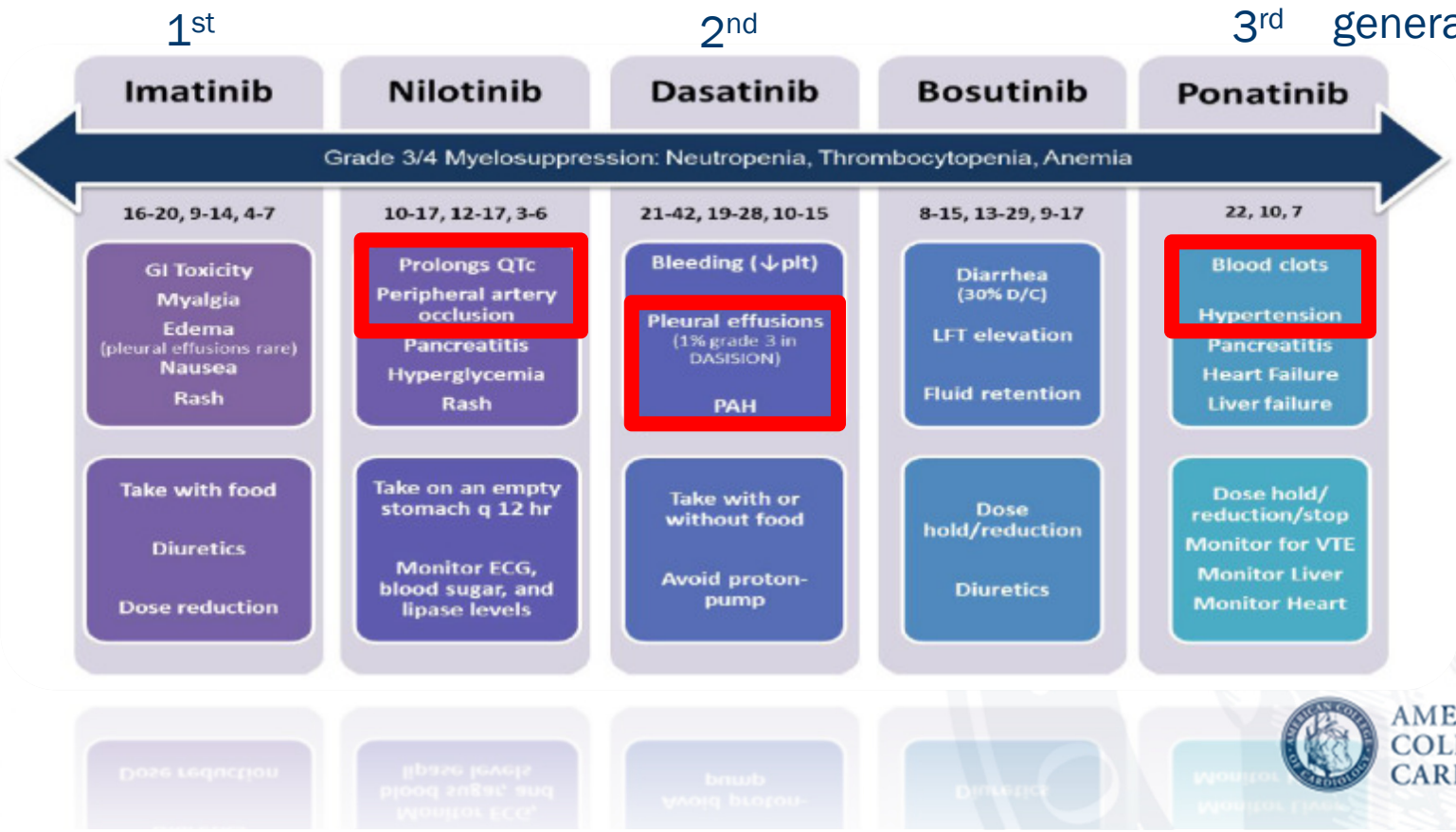
Bcr-Abl TKIs

Generations



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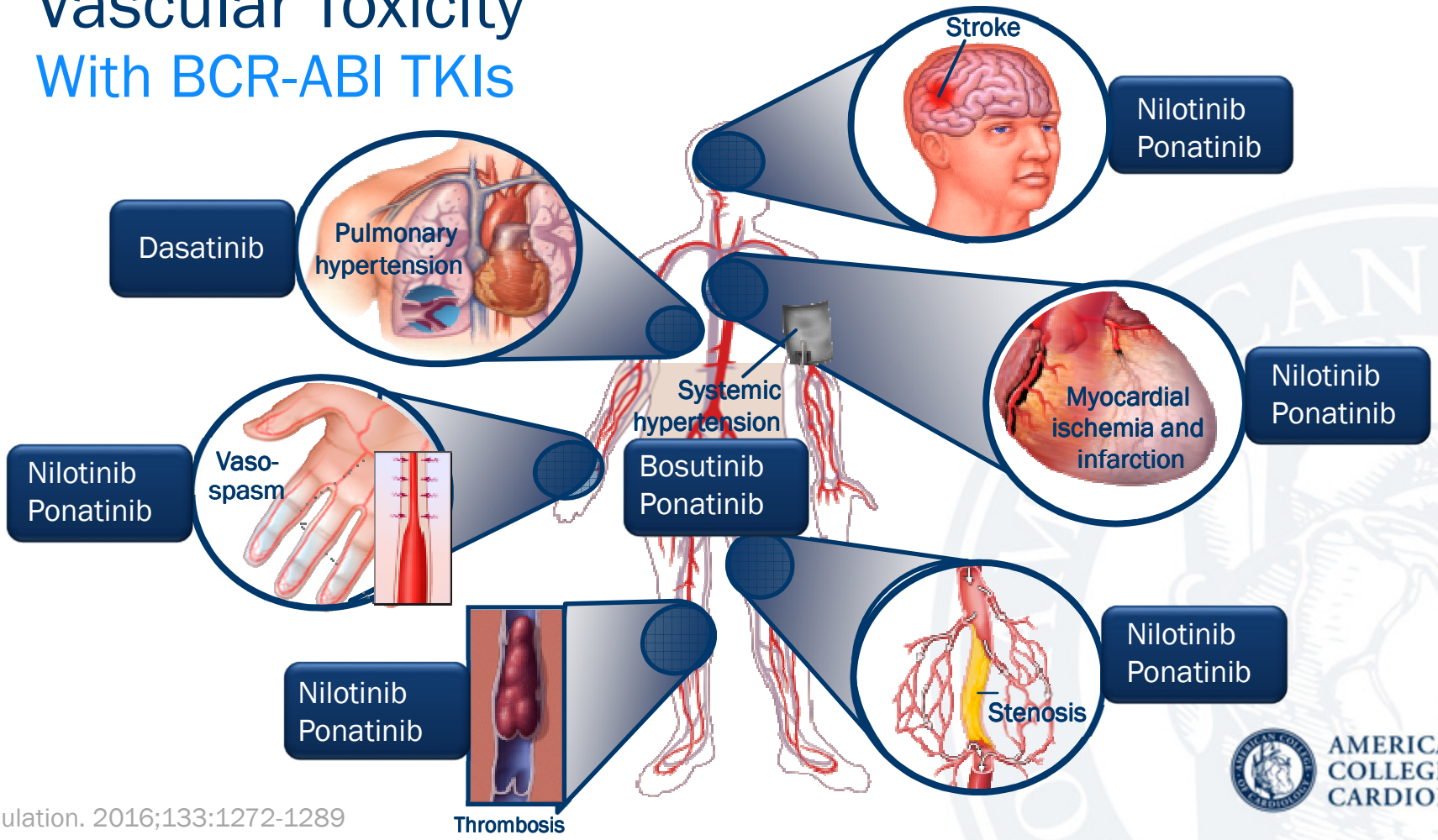
Vascular Toxicity
With BCR-ABL TKIs



Circulation. 2016;133:1272-1289

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Annals of Internal Medicine

ORIGINAL RESEARCH

Cardiovascular Events Associated With Use of Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia

A Population-Based Cohort Study

Torsten Dahlén, MD; Gustaf Edgren, MD, PhD; Mats Lambe, MD, PhD; Martin Höglund, MD, PhD; Magnus Björkholm, MD, PhD; Fredrik Sandin, MSc; Anders Sjöländer, MD, PhD; Johan Richter, MD, PhD; Ulla Olsson-Strömberg, MD, PhD; Lotta Ohm, MD, PhD; Magnus Bäck, MD, PhD; and Leif Stenke, MD, PhD; on behalf of the Swedish CML Group and the Swedish CML Register Group*

Background: Tyrosine kinase inhibitors (TKIs) have increased survival dramatically for patients with chronic myeloid leukemia (CML), but continuous administration of these drugs may elicit

ative risks of 1.5 (95% CI, 1.1 to 2.1) and 2.0 (CI, 1.2 to 3.3), respectively. The event rate for myocardial infarction was higher in patients treated with nilotinib or dasatinib (29 and 19 per 1000

Variable	Imatinib (*n* = 711)			Nilotinib (*n* = 181)			Dasatinib (*n* = 175)		
	Events, *n*	Exposure Time, *y*	Incidence Rate per 1000 Person-Years (95% CI)	Events, *n*	Exposure Time, *y*	Incidence Rate per 1000 Person-Years (95% CI)	Events, *n*	Exposure Time, *y*	Incidence Rate per 1000 Person-Years (95% CI)
All arterial thromboembolic events	31	2405	13 (7–16)	5	170	29 (6–60)	5	262	19 (4–39)
Myocardial infarction	21	2477	8 (4–10)	5	172	29 (6–58)	5	269	19 (4–37)
Cerebrovascular ischemia	9	2503	4 (1–5)	2	175	11 (0–30)	1	276	4 (0–12)
Other arterial thrombosis	3	2545	1 (0–3)	1	176	6 (0–16)	0	282	0 (–)
All venous thromboembolic events	14	2497	6 (2–8)	2	175	11 (0–31)	0	277	0 (–)
Pulmonary embolism	6	2547	2 (0–4)	1	177	6 (0–18)	0	283	0 (–)
Deep venous thrombosis	8	2519	3 (1–6)	1	175	6 (0–20)	0	277	0 (–)
All arterial and venous events	38	2350	16 (11–21)	7	167	42 (15–80)	5	256	20 (4–40)

CML = chronic myelogenous leukemia.
* Patients with events before CML diagnosis were excluded.

deeper molecular response, as measured by quantitative real-time reverse transcription polymerase chain reaction assay of *BCR-ABL1* mRNA; however, long-term follow-up of randomized, controlled trials showed no demonstrable increase in patient survival (4–6). Despite the need for continual oral administration, TKIs are well-tolerated by most patients with CML, and serious toxic events are rare. However, the superiority of

primarily on highly selected patients in clinical trials and on individual case reports, translate into a clinically important increased risk for cardiovascular disease in a broad population of patients with CML treated with TKIs. We therefore analyzed the risk for arterial and venous vascular events in a large population-based cohort of patients with CML treated with first- or second-generation TKIs.

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Vioxx
12.3
8.1

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Abraham NS et al. Aliment Pharmacol Ther 2007;25:913-24

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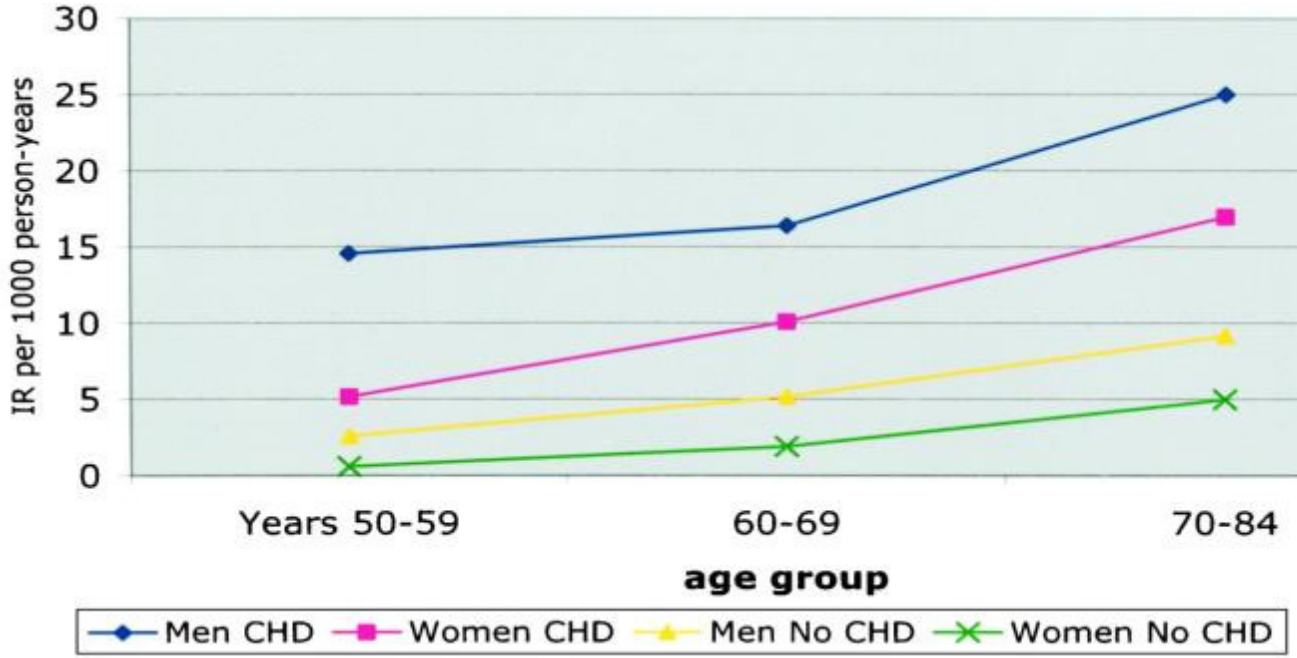
Risk of MI with NSAIDs



General population
5/1000 person-yrs
3.5 w/o CHD
17.2 with CHD

Luis A. García Rodríguez et al. Circulation. 2004;109:3000-3006

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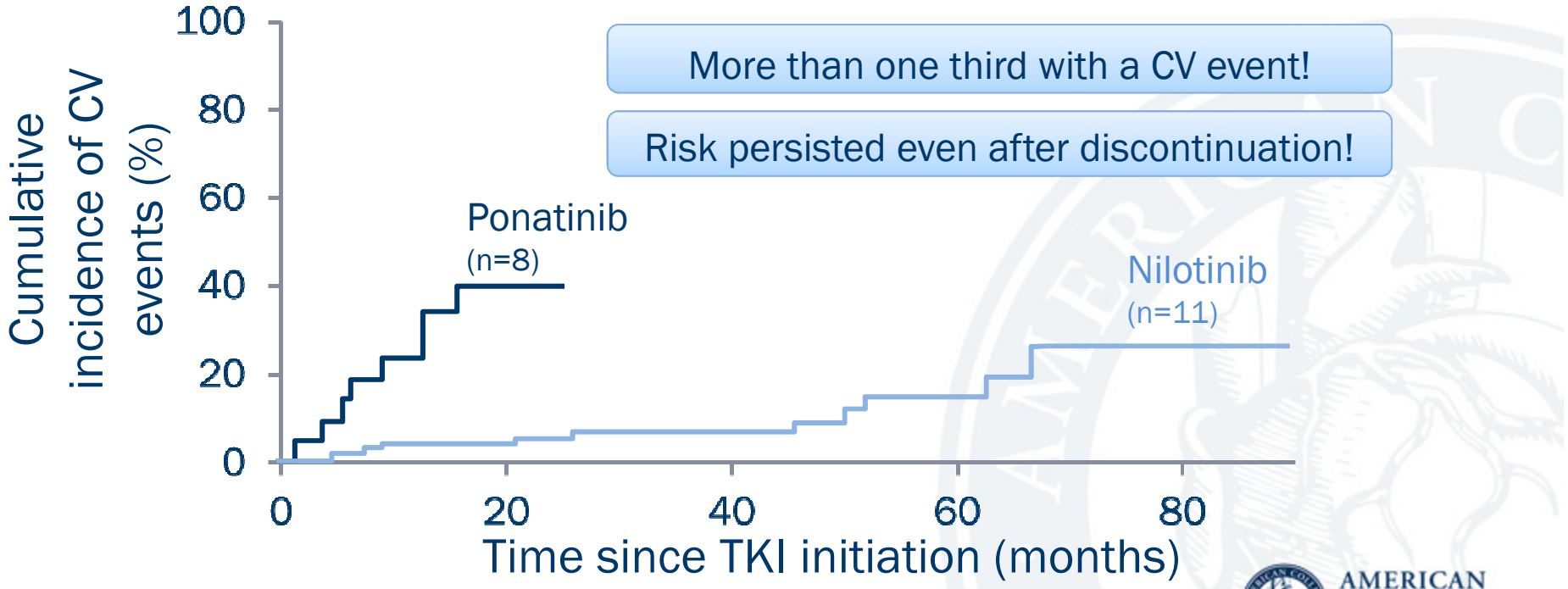
Cardiovascular Events in CML Patients

Ponatinib vs. Nilotinib



Nicolini FE et al. Blood 2013:122:4020

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Vascular Toxicity with Cancer Therapy

Learning Objectives

- To review the spectrum of cardiovascular toxicity with Bcr-Abl Tyrosine Kinase Inhibitor (TKI) therapy for Philadelphia chromosome-positive leukemias
- To evaluate risk prediction approaches
- To formulate risk surveillance and mitigation strategies

Case #1

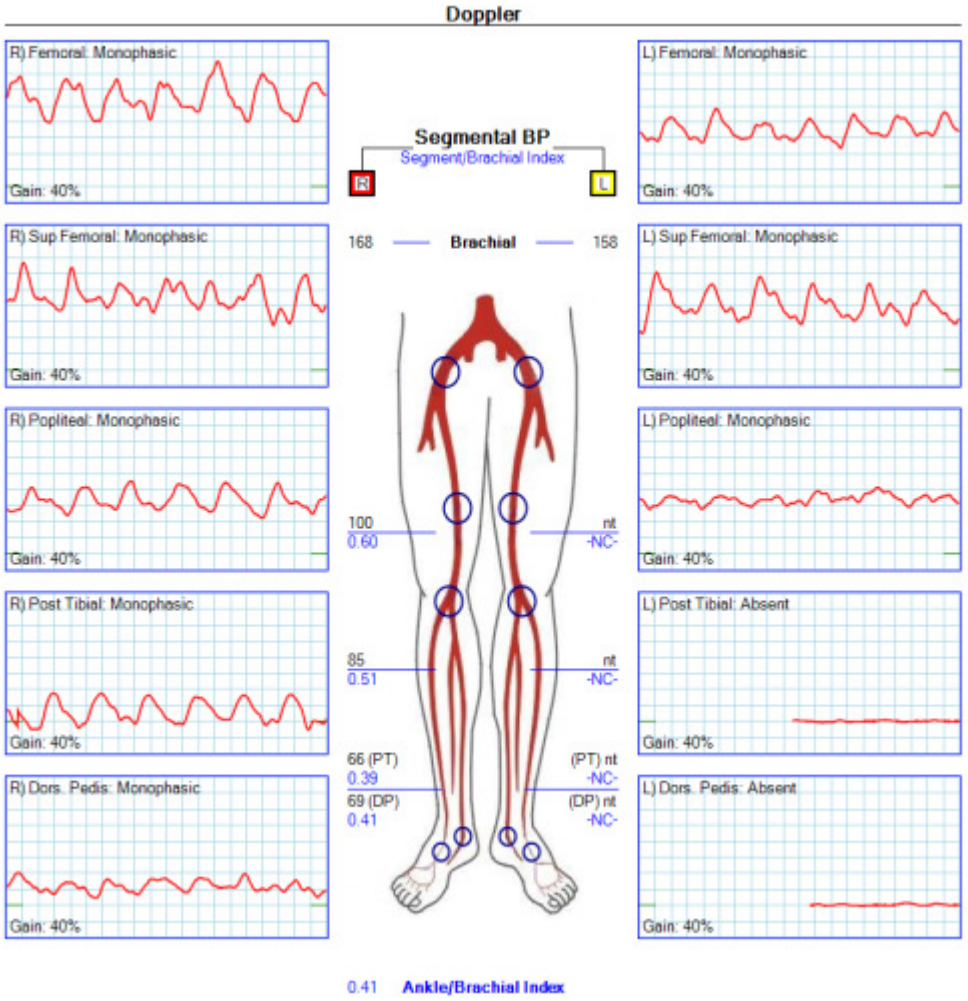
32 year-old female

- Ph+ acute lymphoblastic leukemia
- initially 4 cycles of dasatinib and hyper–CVAD
- rising BCR-ABL transcripts, started ponatinib Feb. 2013, initially at 30 mg, then at 45 mg per day
- excellent cytogenetic and molecular response

Case #1

32 year-old female

- matched unrelated donor allo-HSCT in July 2013
- acute then chronic GVHD, started on sirolimus and prednisone in January 2015
- bluish discoloration of the left lower extremity end of March 2015



Case #1

Doppler Pulse Wave And Ankle/Brachial Index

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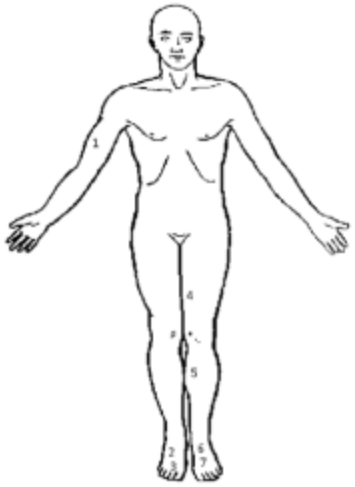
Case #1
Transcutaneous Oximetry



*RPI = Regional Perfusion Index (e.g., 2/1, 3/1, etc), TcPO2's measured in mmHg

Electrode Temperature 45.0°C

	Supine	RPI*
1	88	3
2	51	0.58
3	35	0.40
4	47	0.53
5	21	0.24
6	3	0.03
7	2	0.02

Legs **Elevated** 3 **Minutes**

	Elevated	RPI*
1		4

Dependent 10 **Minutes**

	Dependent	RPI*
1	81	3
2	71	0.88
3	67	0.83
4	60	0.74
5	61	0.75
6	43	0.53
7	31	0.38

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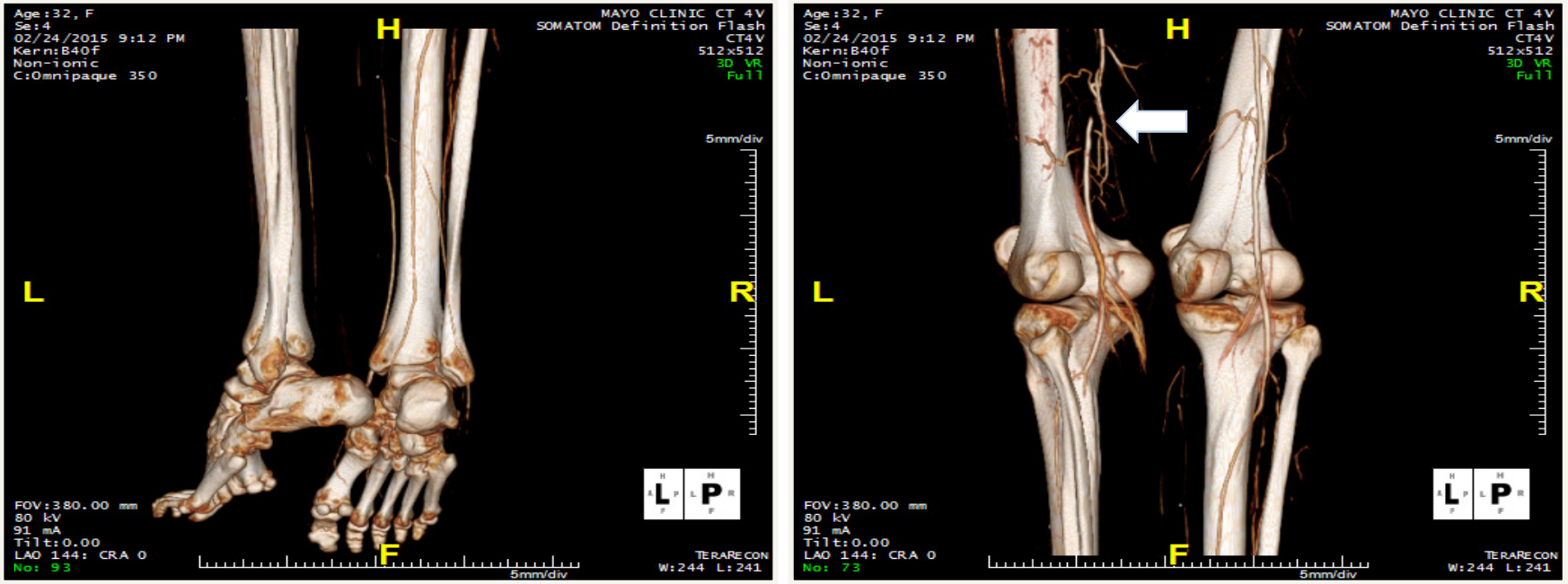
Case #1

Critical Limb Ischemia – SFA occlusion



Herrmann J et al. Mayo Clin Proc 2015;90:1167-8

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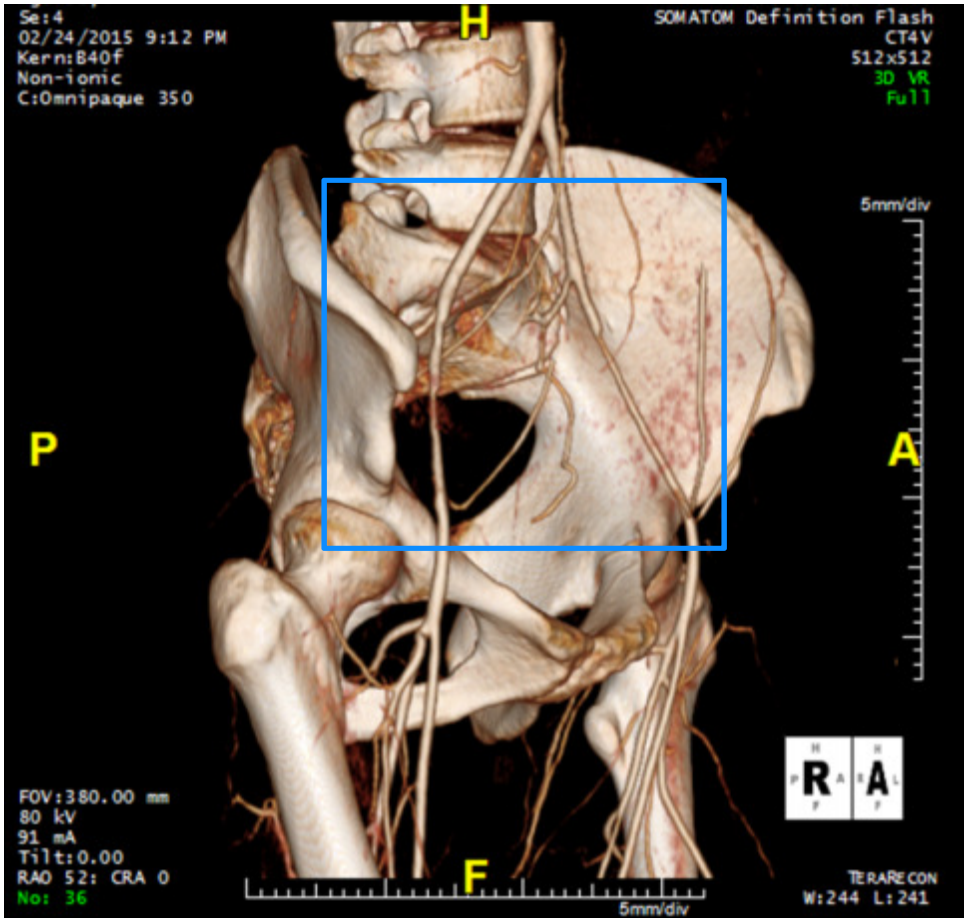

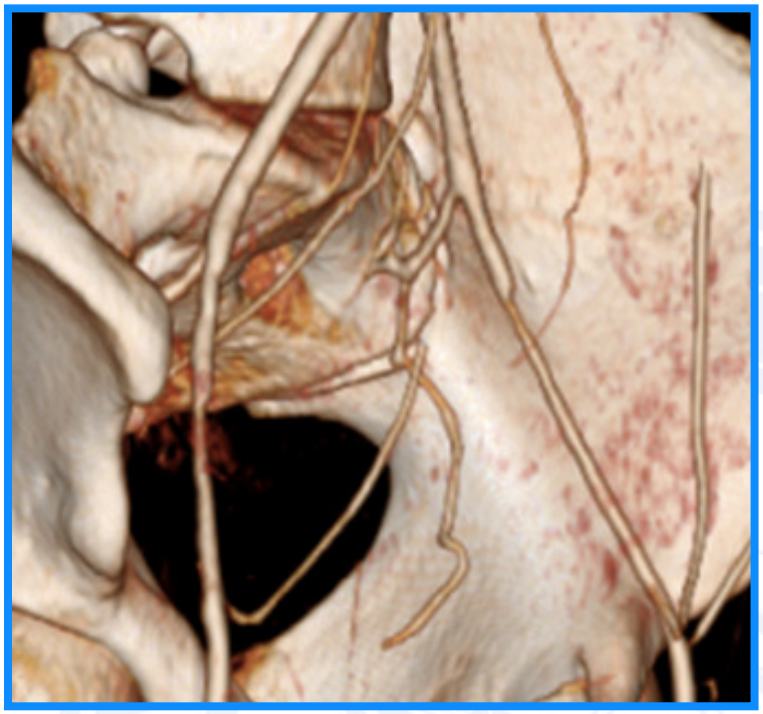

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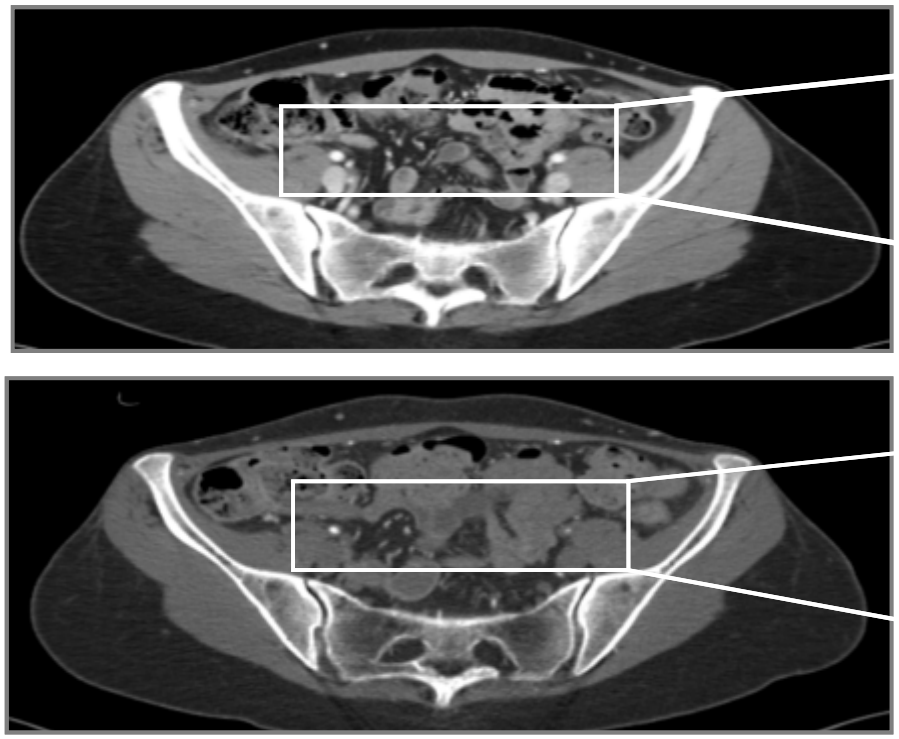
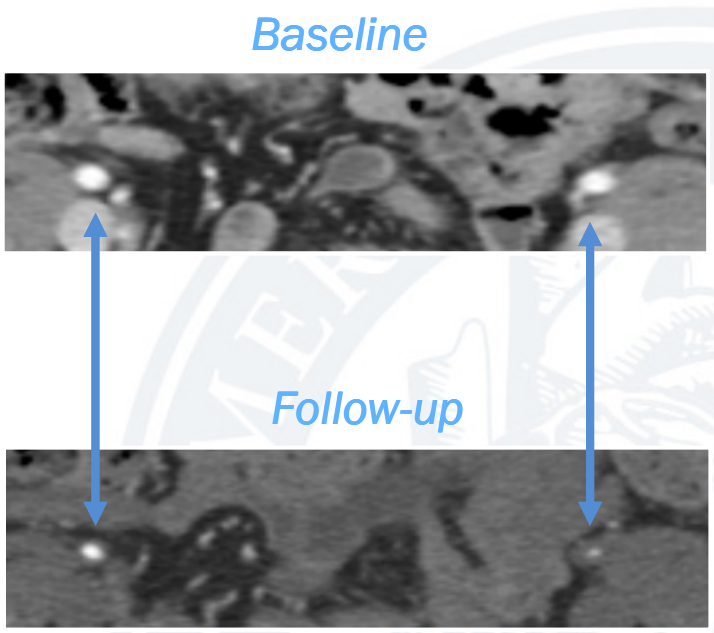
Case #1

Bilateral External Iliac Artery Stenosis





Herrmann J et al. Circulation. 2016;133:1272-1289

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Case #1

What would have been helpful in this case?

A. Baseline CV risk factor assessment (Framingham)

B. Baseline physical including peripheral pulses

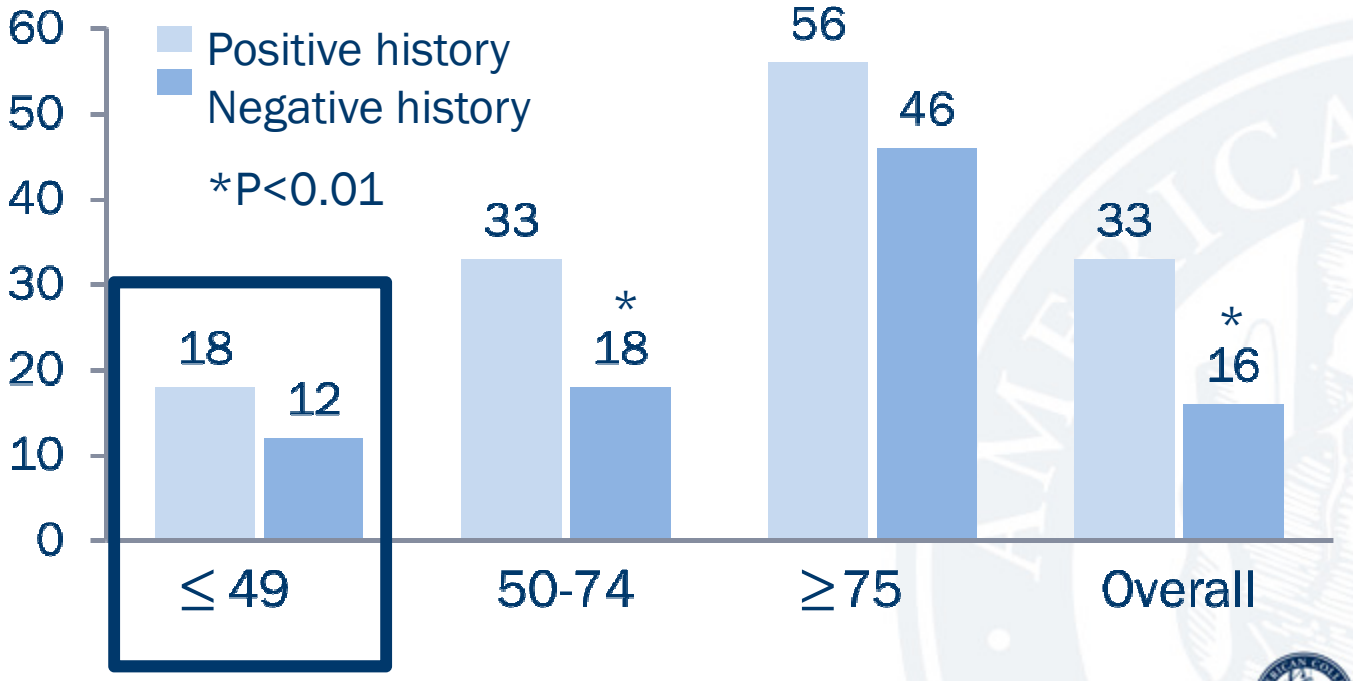
C. Baseline ankle-brachial index

D. Baseline lower extremity Doppler flow evaluation

E. Baseline TcPO2

Risk of Cardiovascular Events With Ponatinib

Stratification by History of IHD, DM, HTN, HLP



Ariad Pharmaceuticals, Inclusig Package Insert

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Relative Risk of Arterial Thrombotic Events With Ponatinib

Risk Category	Arterial SAE Rate in PACE Patients With Risk Category (%)	Arterial SAE Rate in PACE Patients, Excluding Patients With Risk Category (%)	Relative Risk (95% CI)
Age ≥ 65 years	19	11	1.8 (1.2 to 2.9)
History of ischemic cardiac disease	26	10	2.6 (1.6 to 4.0)
Diabetes mellitus	26	11	2.4 (1.5 to 3.8)
Arterial hypertension	20	6	3.2 (1.8 to 5.8)
Hypercholesterolemia	17	10	1.6 (1.0 to 2.7)
No. of cardiac risk factors + history of ischemic disease			
0	6	15	0.4 (0.1 to 1.0)
1	8	15	0.6 (0.3 to 1.1)
≥ 2	18	7	2.5 (1.4 to 4.5)

SAE: 25% at 1.3 years, 50% at 2.7 years (PACE and pre-PACE trial)

Moslehi JJ, Deininger M. J Clin Oncol. 2015;33:4210-8

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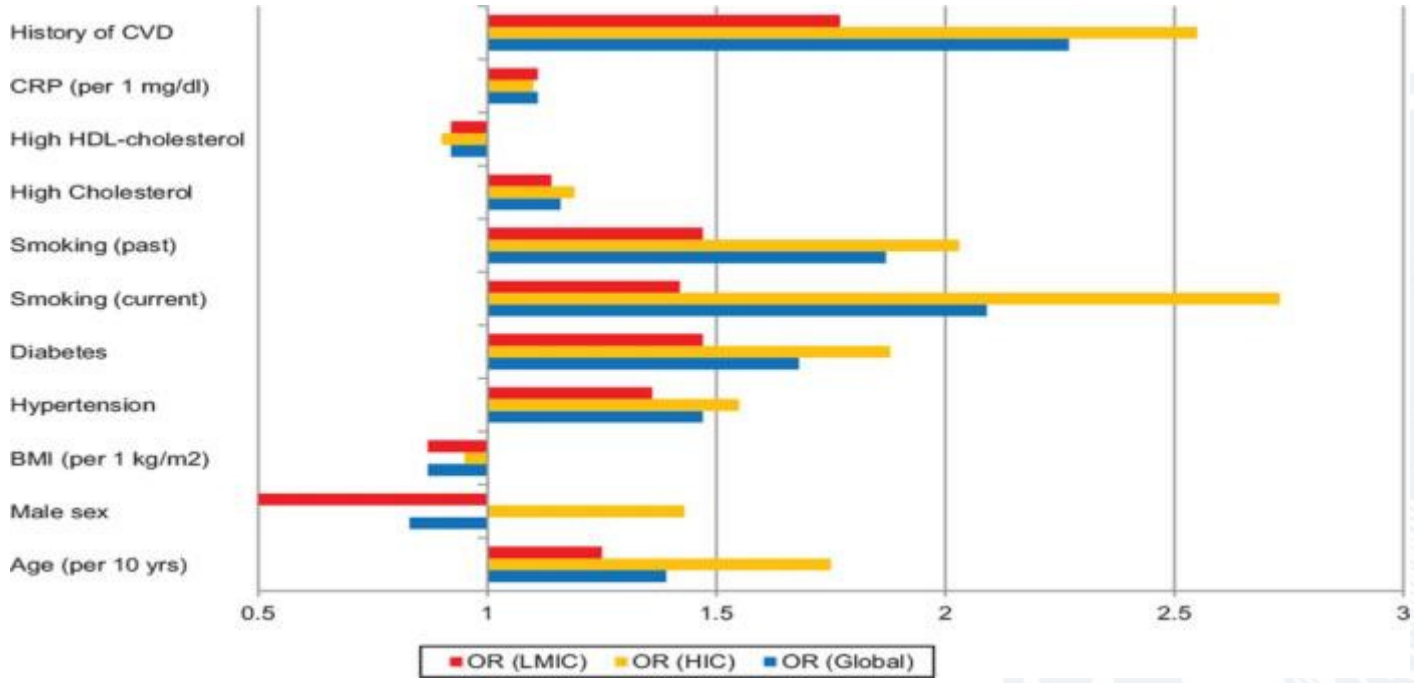
Risk Factors for Peripheral Arterial Disease



Criqui M.H., Aboyans V. Circ Res. 2015;116:1509-1526

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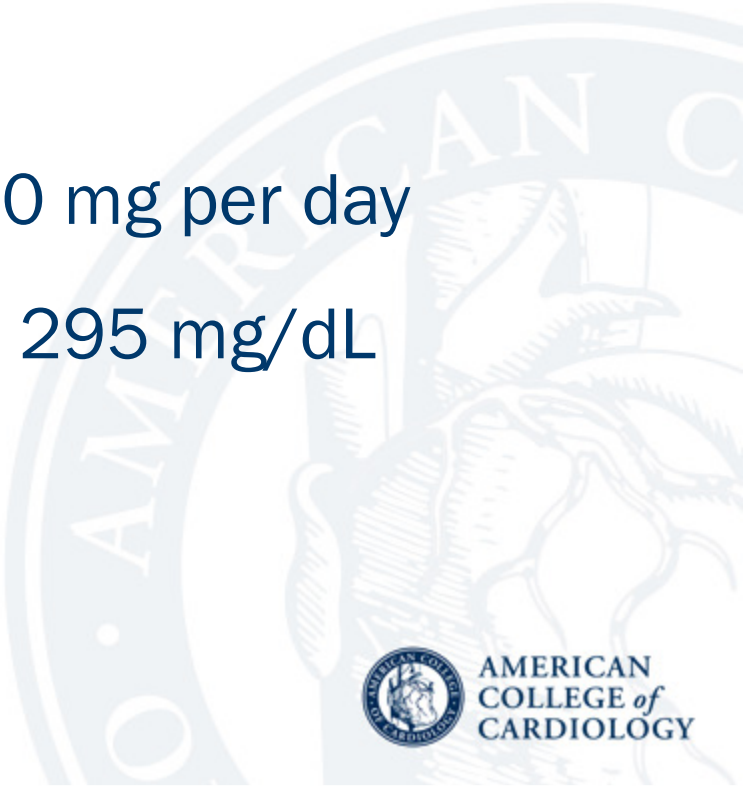
Case #1

32 year-old female

- FRS 0.2%
- BP 150/90 on Lisinopril 10-20 mg per day
- TC 247, HDL 104, LDL 84, TG 295 mg/dL



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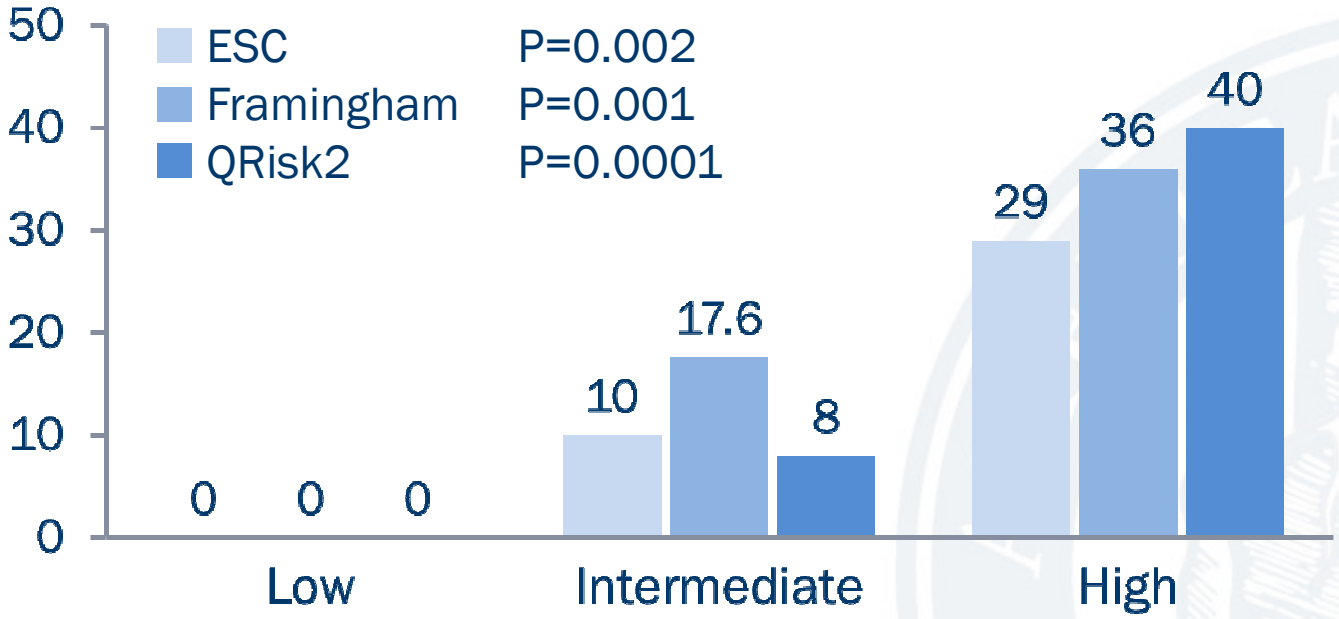
Risk of Cardiovascular Events With Nilotinib

Stratification by CV Risk Scores



Breccia M et al. Ann Hematol. 2015;94:393-7

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journal homepage: www.elsevier.com/locate/critrevonc

Basal assessment

Physical examination

Complete physical evaluation should include:

- Blood pressure
- Heart rate
- Peripheral pulse
- BMI (weight and height)

Medical history

- Previous hemato-oncological disease
- Previous cardiotoxicity due to hemato-oncological treatment
- Respiratory disease
- Ongoing medication

Blood test panel

Blood count, urea, creatinine, uric acid, sodium, potassium, calcium, magnesium, TSH, glucose, HbA_{1C}*, LDL and HDL cholesterol, triglycerides, VES, CRP, fibrinogen, INR

Cardiovascular examination

- ECG with QT and QTcF evaluation
- Echocardiography
- Edinburgh Claudication Questionnaire
- Vascular evaluation *,**,***

*Asymptomatic patients with peripheral pulses and no risk factors may be scheduled for 12 months follow up. **Asymptomatic patients with risk factors or absence of a peripheral pulse should be evaluated by vascular specialist with ankle-brachial index (ABI) [15]. If ABI ≥0.9 a 12 months follow-up should be sufficient, while in patients with ABI <0.9 other tests are mandatory, such as lower limbs and carotid ultrasound and a 6 months follow-up. **Anyway, measurement of carotid intima-media thickness and/or screening for atherosclerotic disease by carotid artery ultrasound should be considered in asymptomatic adults at moderate risk [13].** ***Symptomatic patient for *claudicatio intermittens* should be evaluated by vascular specialist with ABI and their follow-up with echocolor-doppler can be scheduled on 3 or 6 months with ABI <0.7 for cut off.

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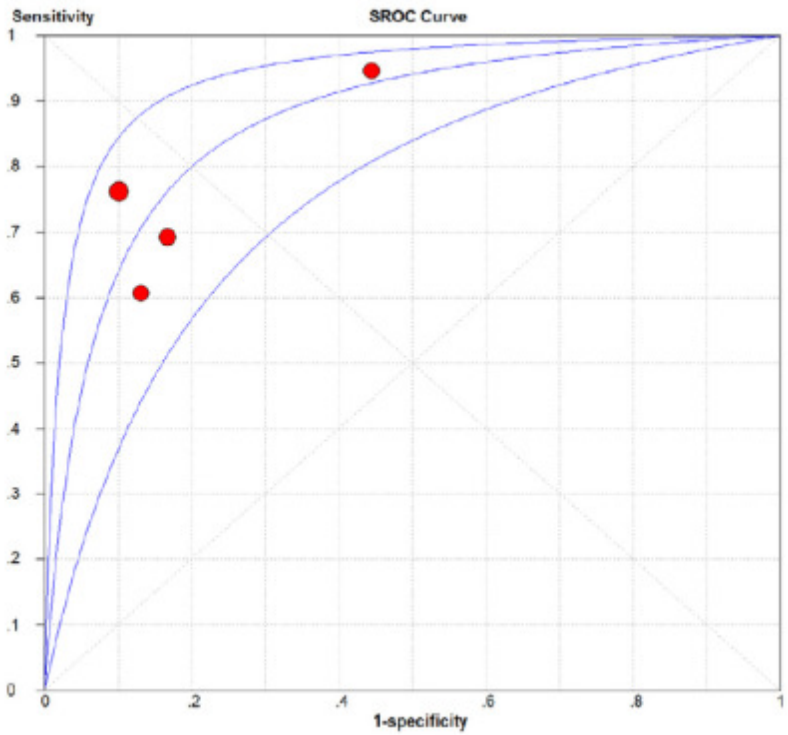
History and Physical Examination for PAD

Symptoms/findings	Prevalence	Sensitivity	Specificity	Predictive value +	Predictive value −
Rose claud.	1.9	9.2	99.0	54.5	89.5
Rose or poss. claud.	5.9	20.0	95.9	38.2	90.4
Femoral bruit	6.0	20.0	95.7	36.7	90.7
Abn. femoral pulse	3.0	12.7	98.2	46.7	90.1
Abn. post. tibial pulse	15.1	71.2	91.3	48.7	96.5
Abn. dorsalis pedis pulse	29.3	50.0	73.1	17.7	92.7
Any abn. pulse^	20.1	76.9	86.4	39.6	97.0
Rose or any abn. pulse	21.3	78.2	85.6	39.8	97.0
Rose or poss. or any abn. pulse	24.1	82.1	83.1	37.4	97.4
Rose and any abn. pulse	0.9	4.8	99.6	60.0	89.8
Rose or poss. and any abn. pulse	2.2	11.5	98.8	53.8	90.5

^Dorsalis pedis abnormalities excluded.

Criqui M.H. et a. Circ 1985;71;516-22

Diagnostic Performance of ABI for PAD (>50% stenosis)



Pooled sensitivity
0.75 (0.71-0.79)

Pooled specificity
0.86 (0.83-0.90)

Pooled positive LR
4.18 (2.14-8.14)

Pooled negative LR
0.29 (0.18-0.47)

Standard deviation of difference between 2 separate measures: 0.08

Variability 10%

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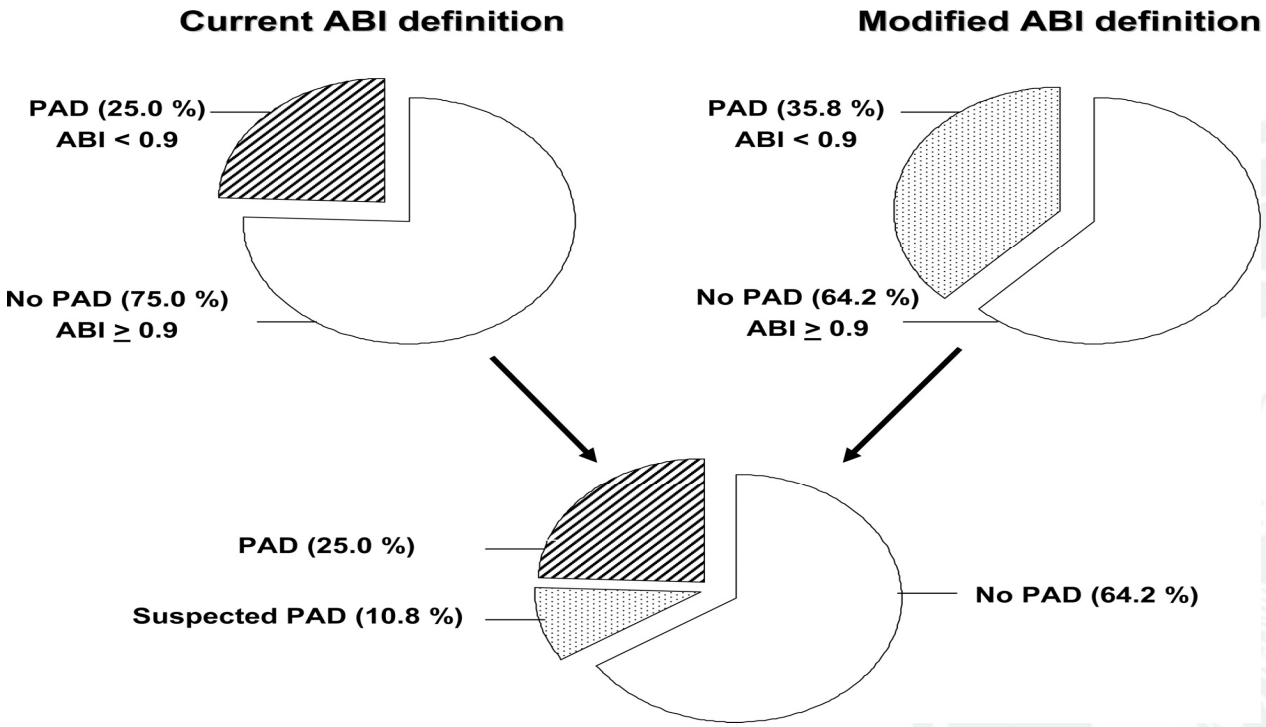
Xu D et al. Can J Cardiol 2013;29:492-8

Van Langen H et al. Vasc Med 2009;14:221-6

Correlation ABI and Extent of PAD

Clinical status	ABI	TBI or Toe systolic pressure
Normal	0.9-1.2	0.8-0.9
Mild	0.8-0.9	60 – 80 mmHg
Moderate-severe	0.4-0.8	40 – 60 mmHg
Resting ischemia	<0.4	<0.15 or <30 mmHg
Tissue loss	<0.5	40 mmHg
Threatened limb	<0.15	0
Medial calcification	>1.3	Commonly unaffected

Higher vs. Lower Ankle Blood Pressure for ABI



Christine Espinola-Klein et al. Circulation. 2008;118:961-967

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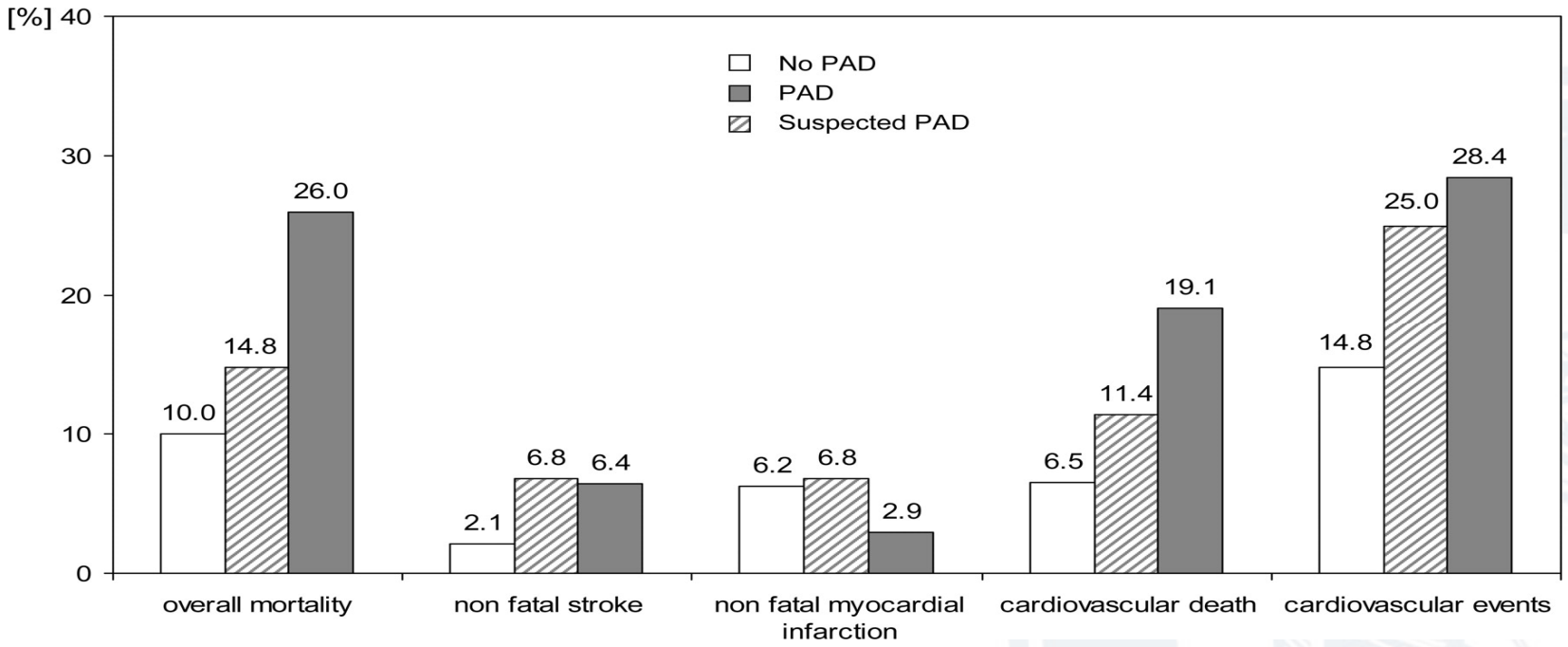
Lower Ankle ABI and Outcomes



Christine Espinola-Klein et al. Circulation. 2008;118:961-967

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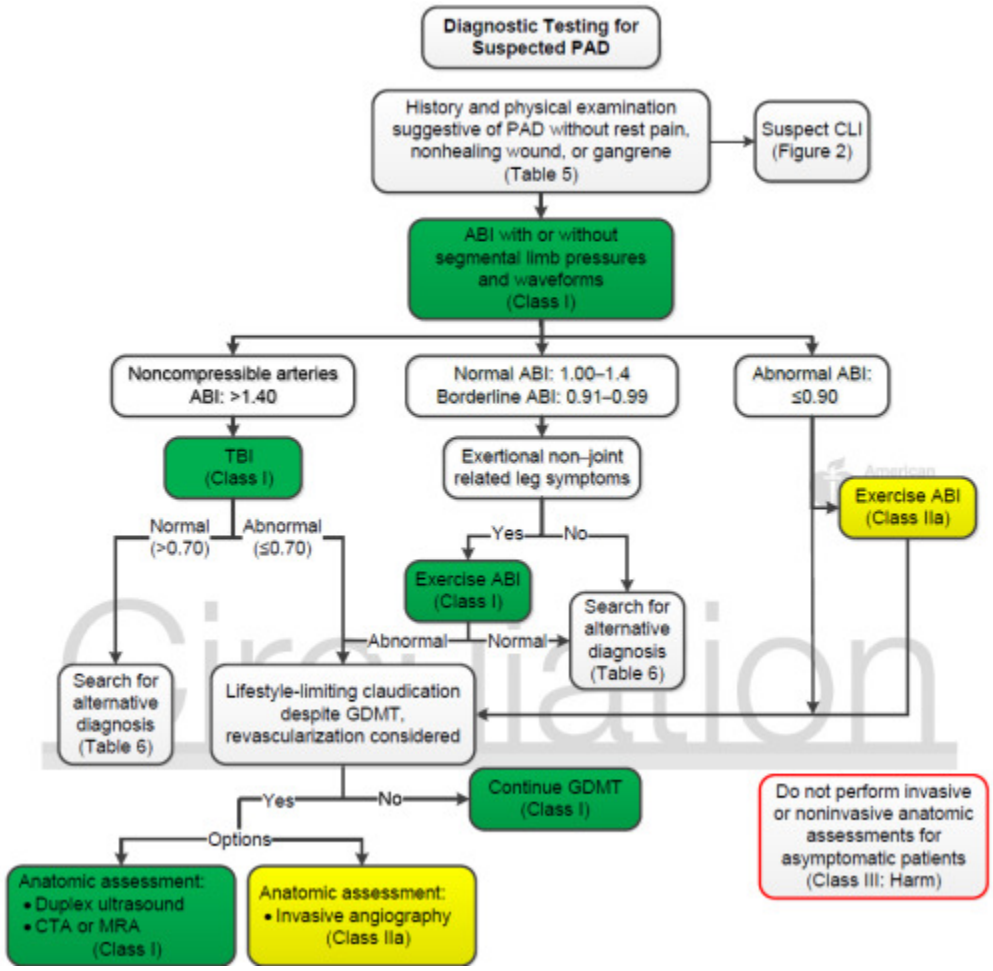

Gerhard-Herman MD et al. 2016 AHA/ACC Lower Extremity PAD Guideline

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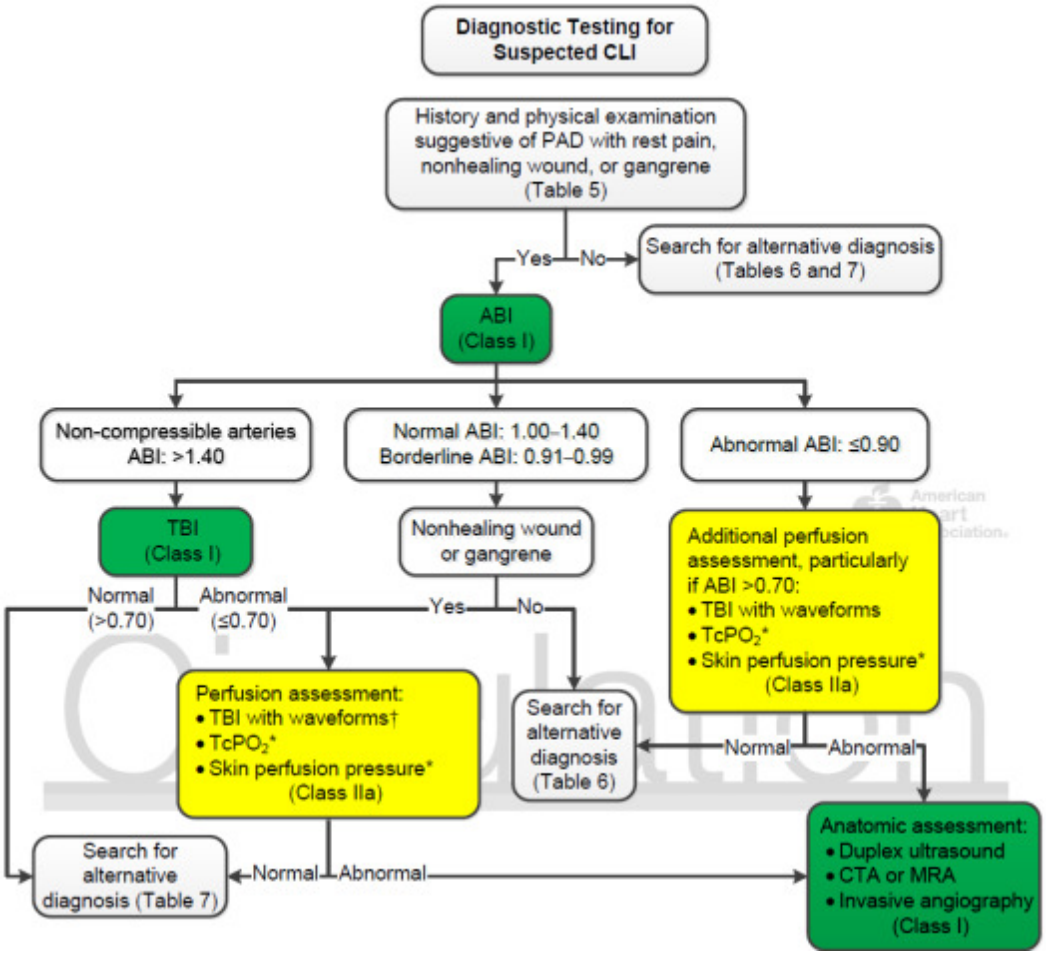

Gerhard-Herman MD et al. 2016 AHA/ACC Lower Extremity PAD Guideline

Case #1

Would you recommend any follow-up evaluation?

A. No

B. Follow-up physical every 3-6 months

C. Follow-up physical every 12 months

D. Follow-up ABI every 3-6 months

E. Follow-up ABI every 12 months

Provisional Follow-Up Recommendations

Assessment	Imatinib	Nilotinib	Dasatinib	Bosutinib	Ponatinib
Baseline	Follow good clinical practice				
Clinical cardiovascular assessment, including blood pressure		REC	REC	REC	REC
Fasting glucose		REC	ACI	ACI	REC
Fasting lipid p					REC
Echocardiogra					ACI
ECG					ACI
Ankle-brachial					REC
1-month follow-u					
Clinical cardiov					REC
Blood pressur					REC
3- to 6-month fo					
Clinical cardiov					REC
Blood pressur					REC
Fasting glucos					ACI
Fasting lipid p					REC
Echocardiogram		ACI	ACI*	ACI	ACI
ECG		ACI†	ACI	ACI	ACI
Ankle-brachial index		REC	ACI	ACI	REC

What is the expected timeline and pace of progression?

NOTE. Practice guidelines regarding prevention of cardiovascular toxicity should be followed, including tobacco cessation counseling. In symptomatic patients or those with high cardiovascular risk, consider referral to cardiologist.
Abbreviations: ACI, as clinically indicated; ECG, electrocardiogram; REC, recommended; TKI, tyrosine kinase inhibitor.
*Low threshold for an echocardiogram in patient considered for treatment or being treated with dasatinib who has cardiopulmonary symptoms.
†ECG prior to starting, after 7 days after starting, and after each dose change (package insert).

Moslehi JJ, Deininger M. J Clin Oncol. 2015;33:4210-8

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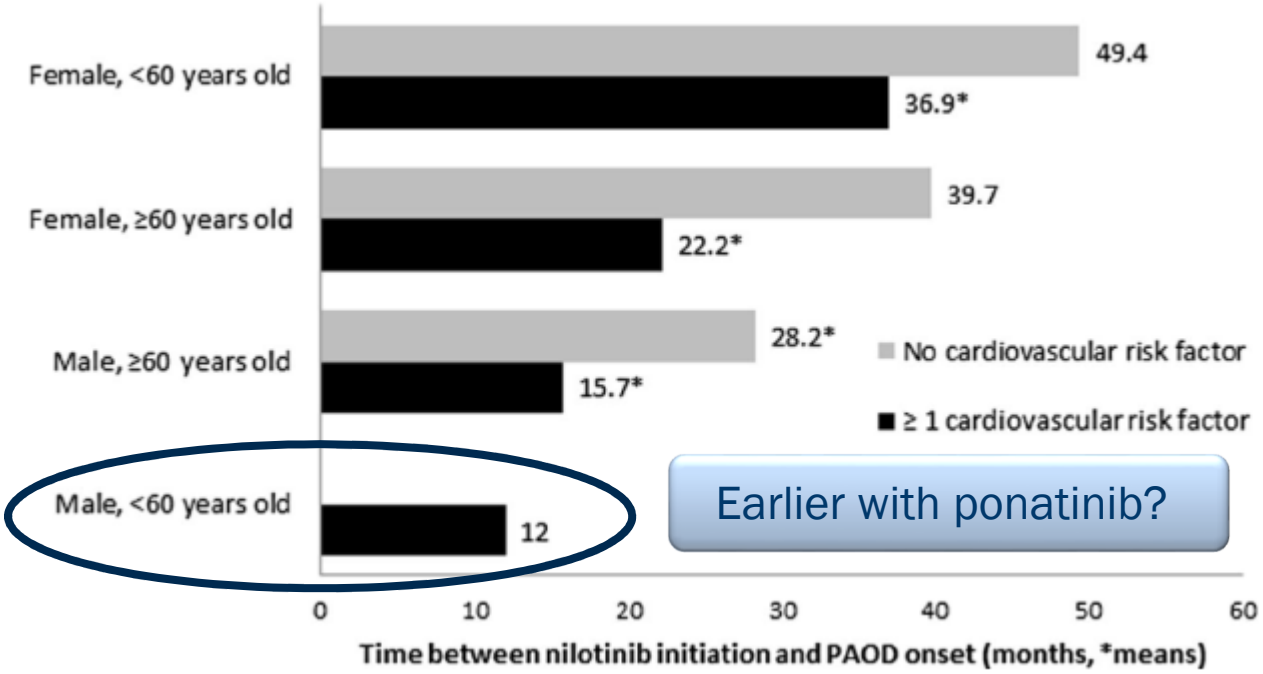
Average Time to PAD Onset on Nilotinib



Bondon-Guitton E et al.: Targ Oncol 11:549, 2016

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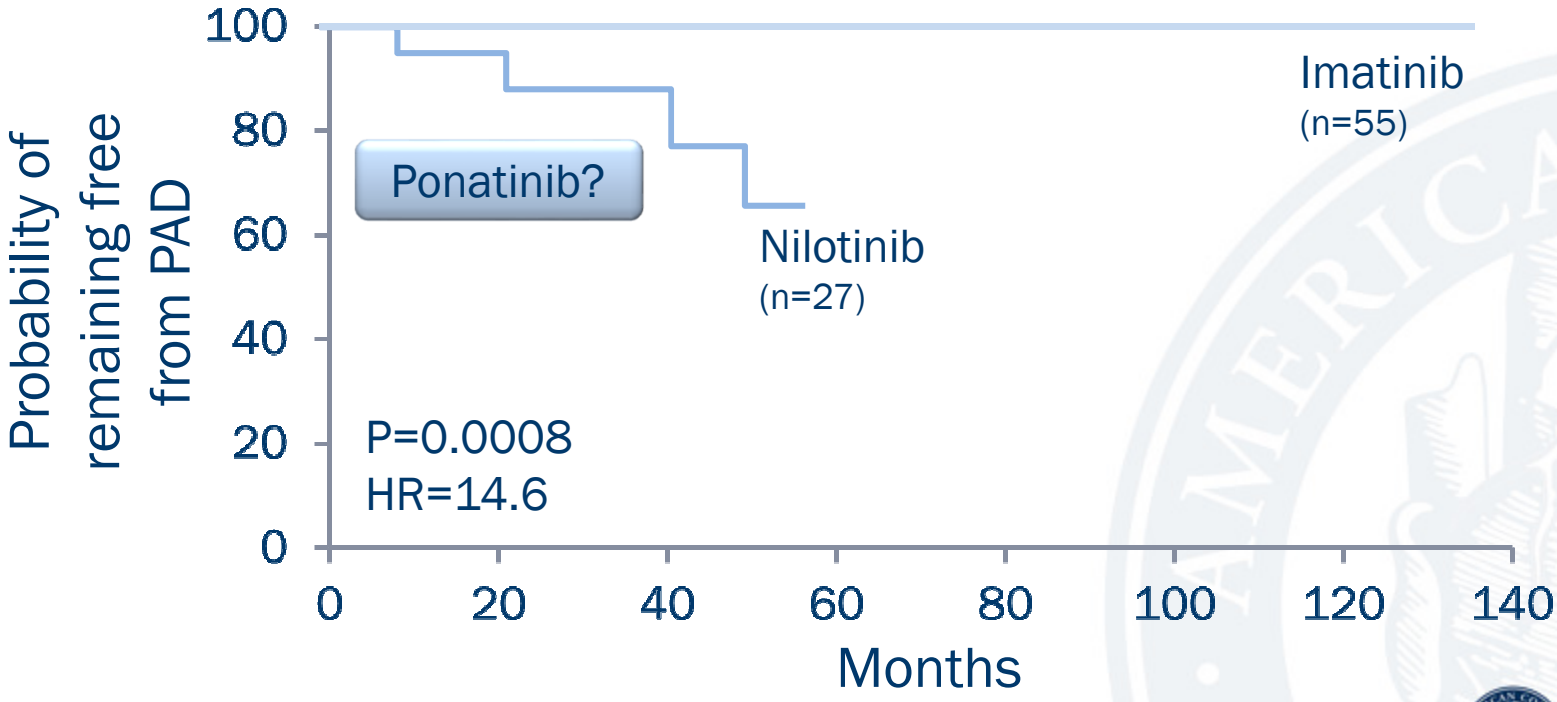
Clinical PAD

Nilotinib vs. Imatinib



Levato L et al. Eur J Haematol. 2013;90:531-2

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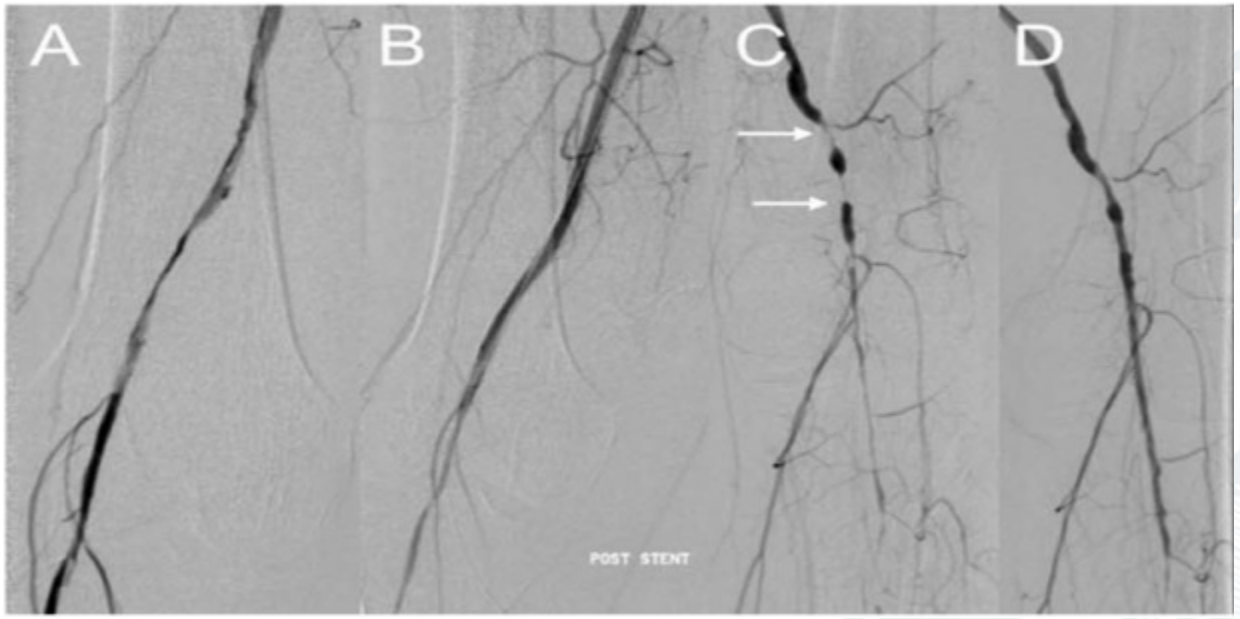
Diffuse Progressive ASCVD with Nilotinib

Peripheral Arterial Disease



Aichberger K.J. et al. Am J Hematol 2011;86:533

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Provisional Follow-Up Recommendations

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Baseline	Follow good clinical practice				
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Fasting glucose		REC	ACI	ACI	REC
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Echocardiogra					ACI
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Ankle-brachial					REC
1-month follow-u					
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Blood pressur					REC
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Clinical cardiov					REC
Blood pressur					REC
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Echocardiogram		ACI	ACI*	ACI	ACI
ECG		ACI†	ACI	ACI	ACI
Ankle-brachial index		REC	ACI	ACI	REC

NOTE. Practice guidelines regarding prevention of cardiovascular toxicity should be followed, including tobacco cessation counseling. In symptomatic patients or those with high cardiovascular risk, consider referral to cardiologist.
Abbreviations: ACI, as clinically indicated; ECG, electrocardiogram; REC, recommended; TKI, tyrosine kinase inhibitor.
*Low threshold for an echocardiogram in patient considered for treatment or being treated with dasatinib who has cardiopulmonary symptoms.
†ECG prior to starting, after 7 days after starting, and after each dose change (package insert).

What is the time frame to detection - 3 months or 6 months every year, or only in the 1st year, dependent on vary type of TKI?

Moslehi JJ, Deininger M. J Clin Oncol. 2015;33:4210-8

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Provisional Follow-Up Recommendations

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Echocardiogram		ACI	ACI*	ACI	ACI
ECG		ACI†	ACI	ACI	ACI
Ankle-brachial index		REC	ACI	ACI	REC

What is the cutoff for detection – 0.02 at 6 months, any decline?

NOTE. Practice guidelines regarding prevention of cardiovascular toxicity should be followed, including tobacco cessation counseling. In symptomatic patients or those with high cardiovascular risk, consider referral to cardiologist.
Abbreviations: ACI, as clinically indicated; ECG, electrocardiogram; REC, recommended; TKI, tyrosine kinase inhibitor.
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Moslehi JJ, Deininger M. J Clin Oncol. 2015;33:4210-8

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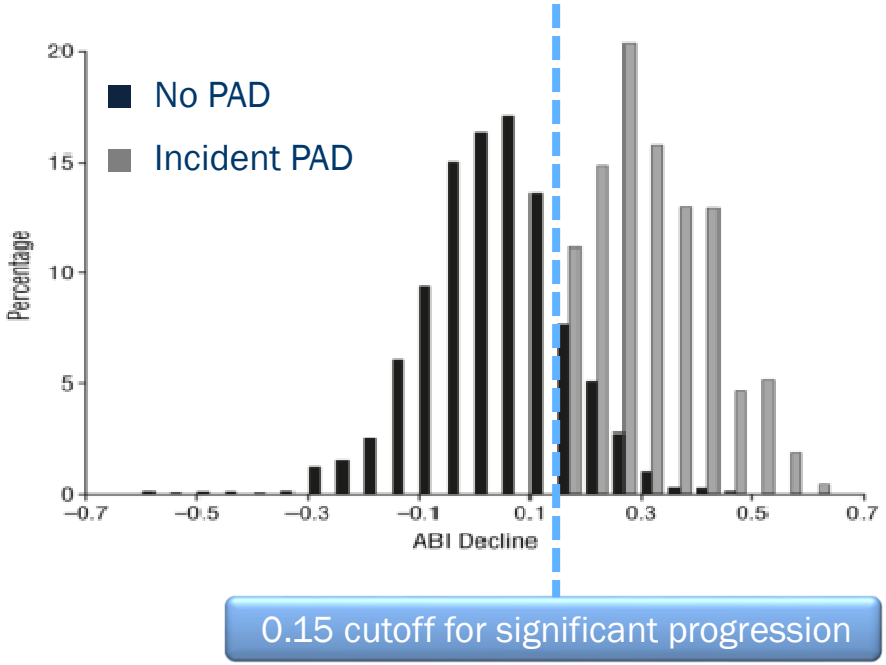
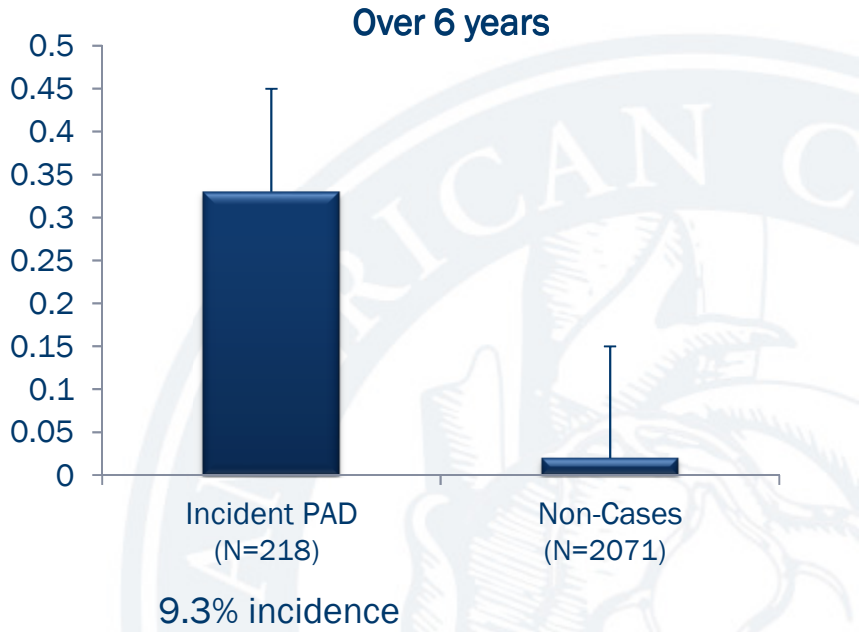
Spectrum of ABI Decline





Arch Intern Med. 2005;165:1896-1902

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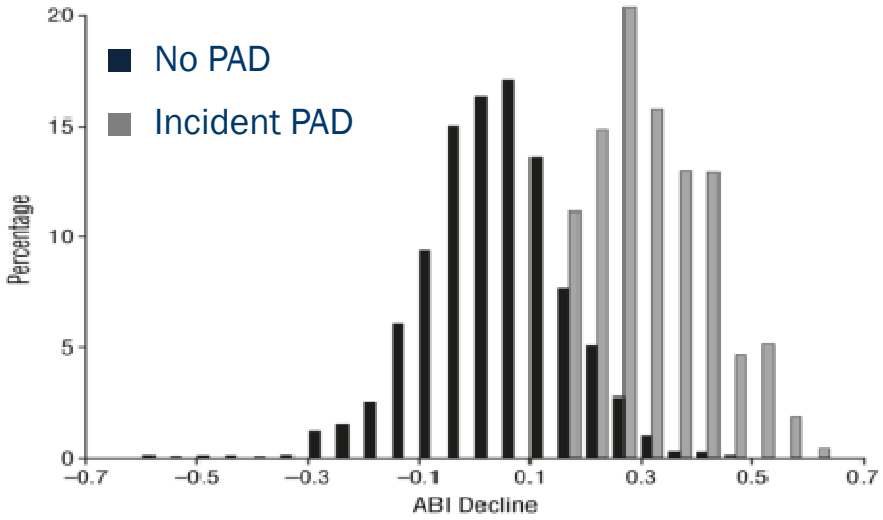
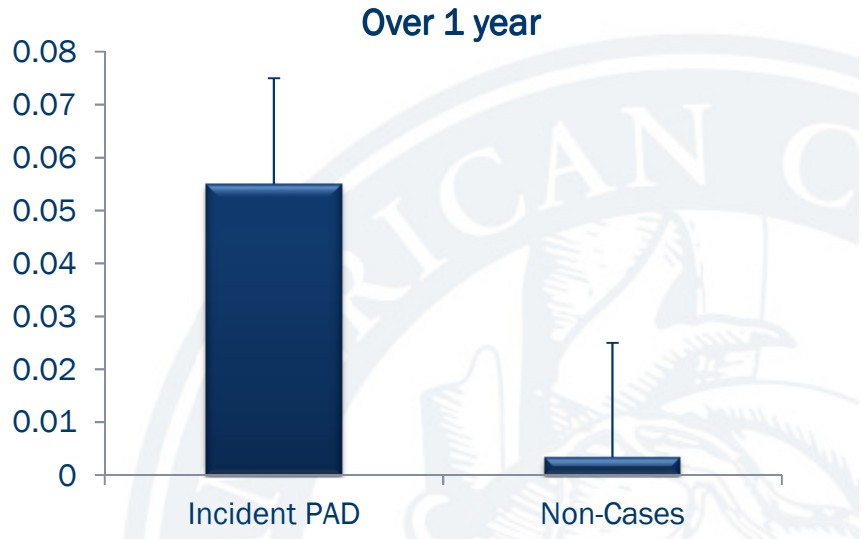
Spectrum of ABI Decline





Arch Intern Med. 2005;165:1896-1902

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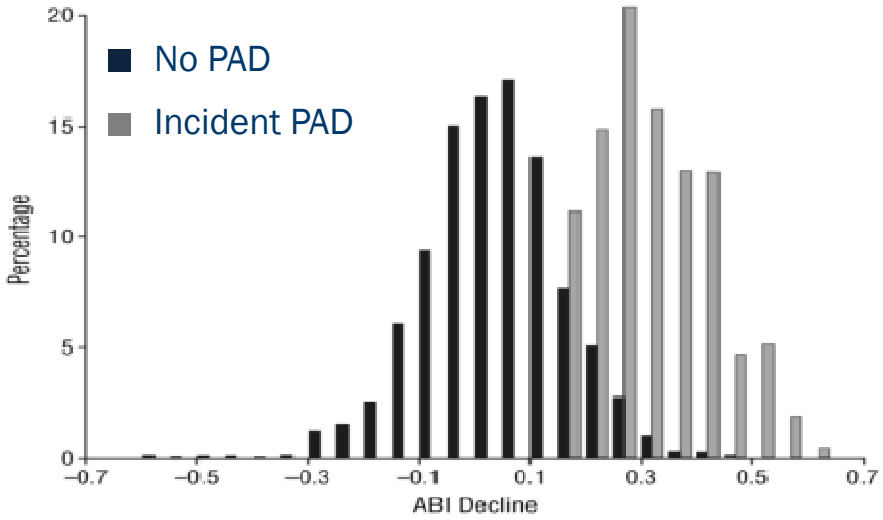
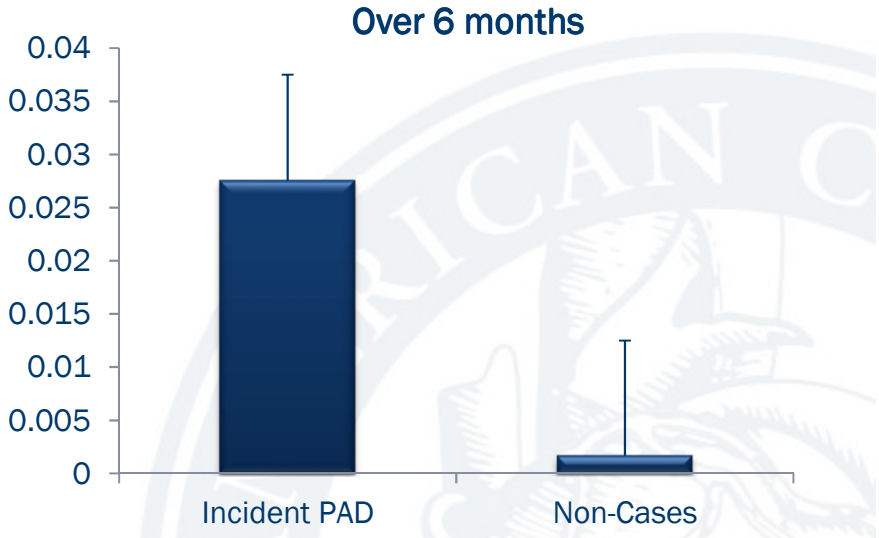
Spectrum of ABI Decline





Arch Intern Med. 2005;165:1896-1902

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Questions Raised

- What can be predicted by ABI?
- Does a normal test exclude risk,

  does an abnormal test prohibit therapy?
- Which additional tests should these patients have?
- Should this be done routinely or only in a subset?

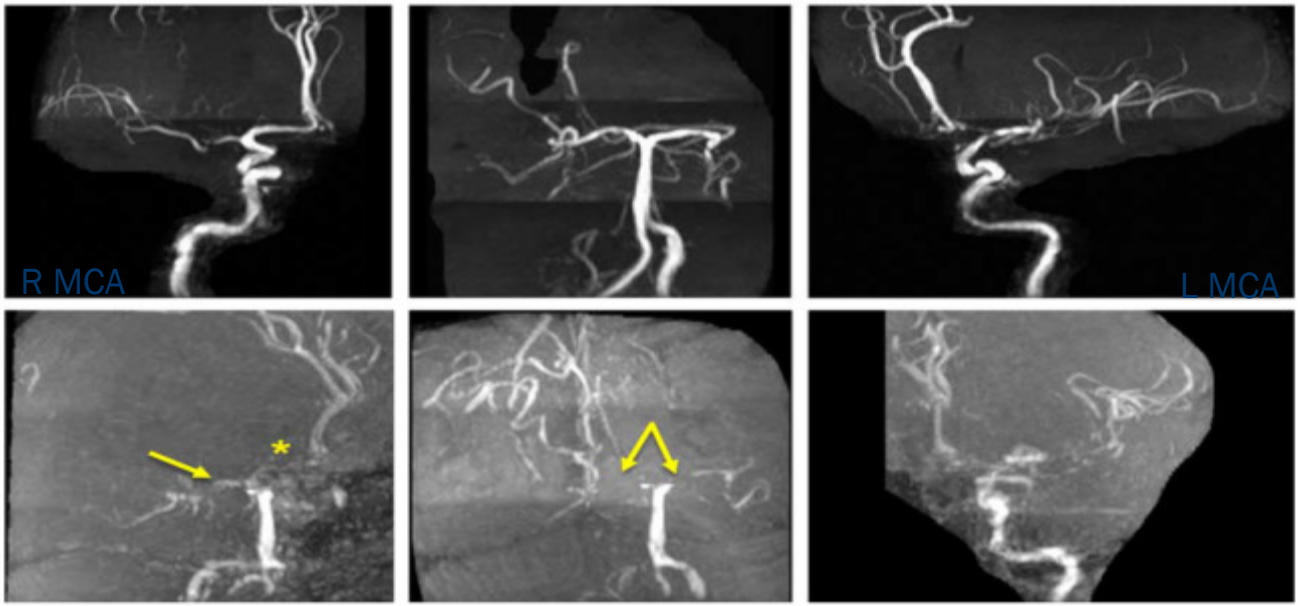
Diffuse Progressive ASCVD with Nilotinib

Acute Right-Hemispheric Stroke

70 yo female w/CML, on nilotinib since 2004 w/PAD + CAD

2011

2012



Coon E.A. et al. Am J Hematol 2013;86:534-5

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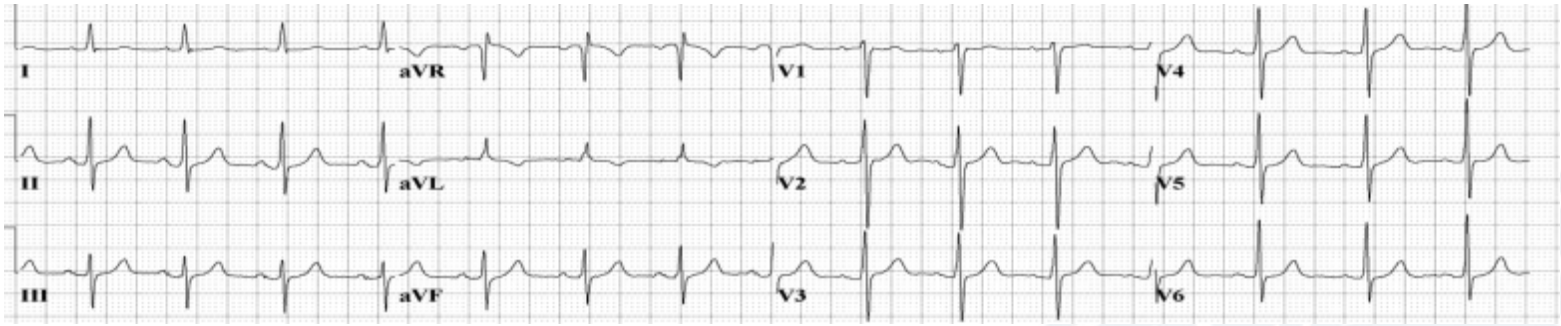
Case #1 continued
32 year-old female

- bilateral external iliac artery stenting and left SFA recanalization, started on DAPT
- development of left lower extremity compartment syndrome, requiring fasciotomy
- acute chest pain on post-op day #2

Baseline



Acute chest pain

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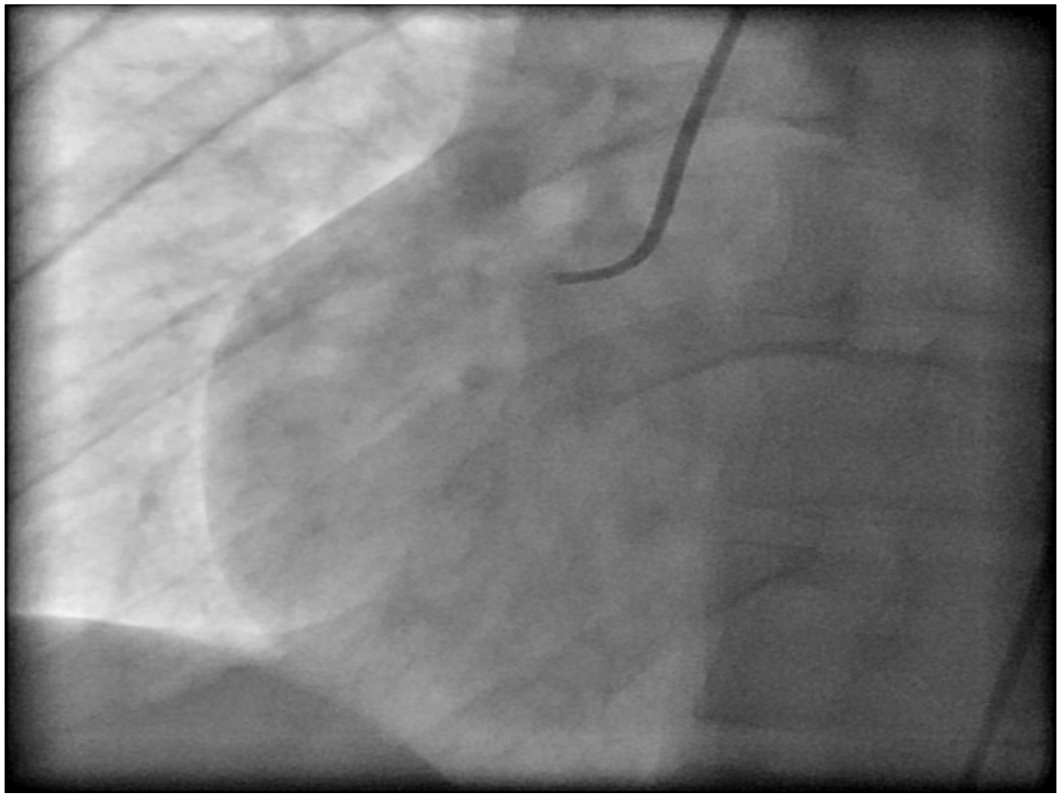
Case #1



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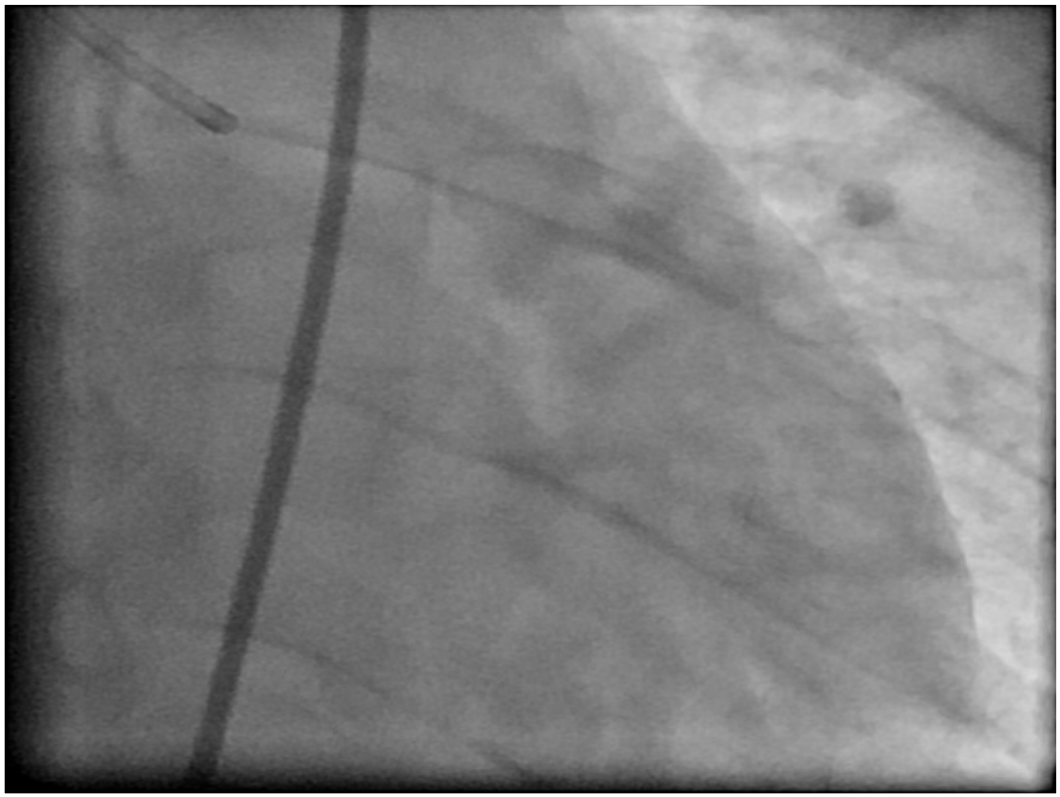
Case #1



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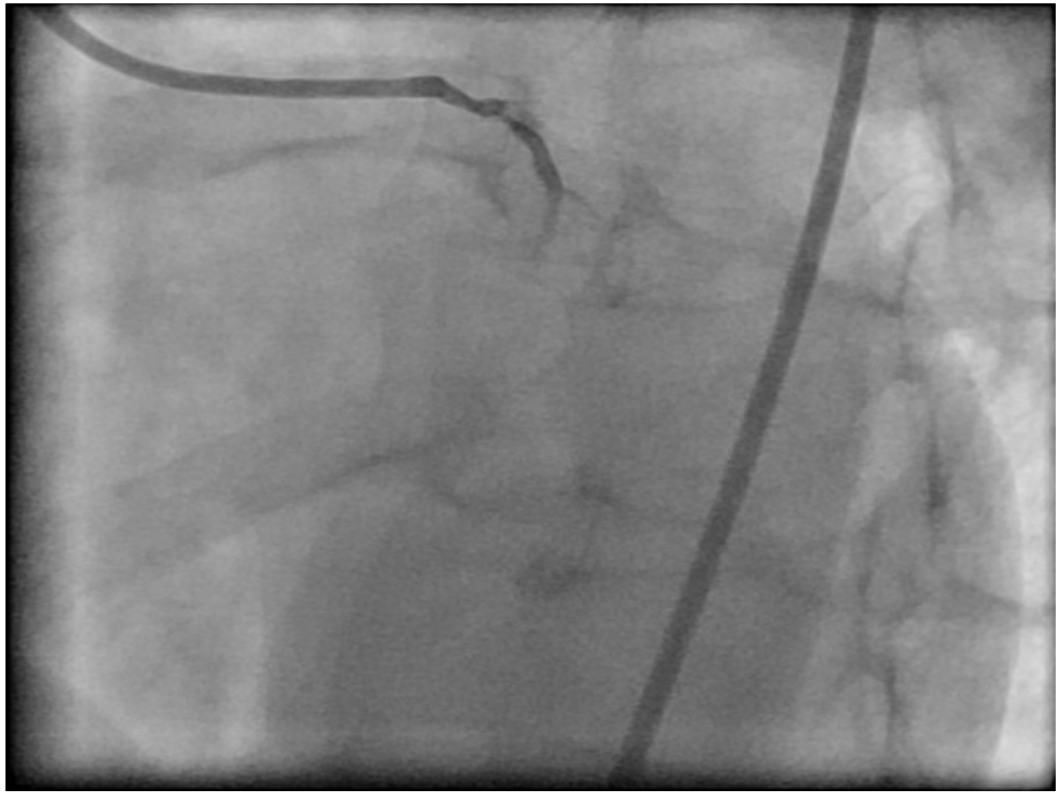
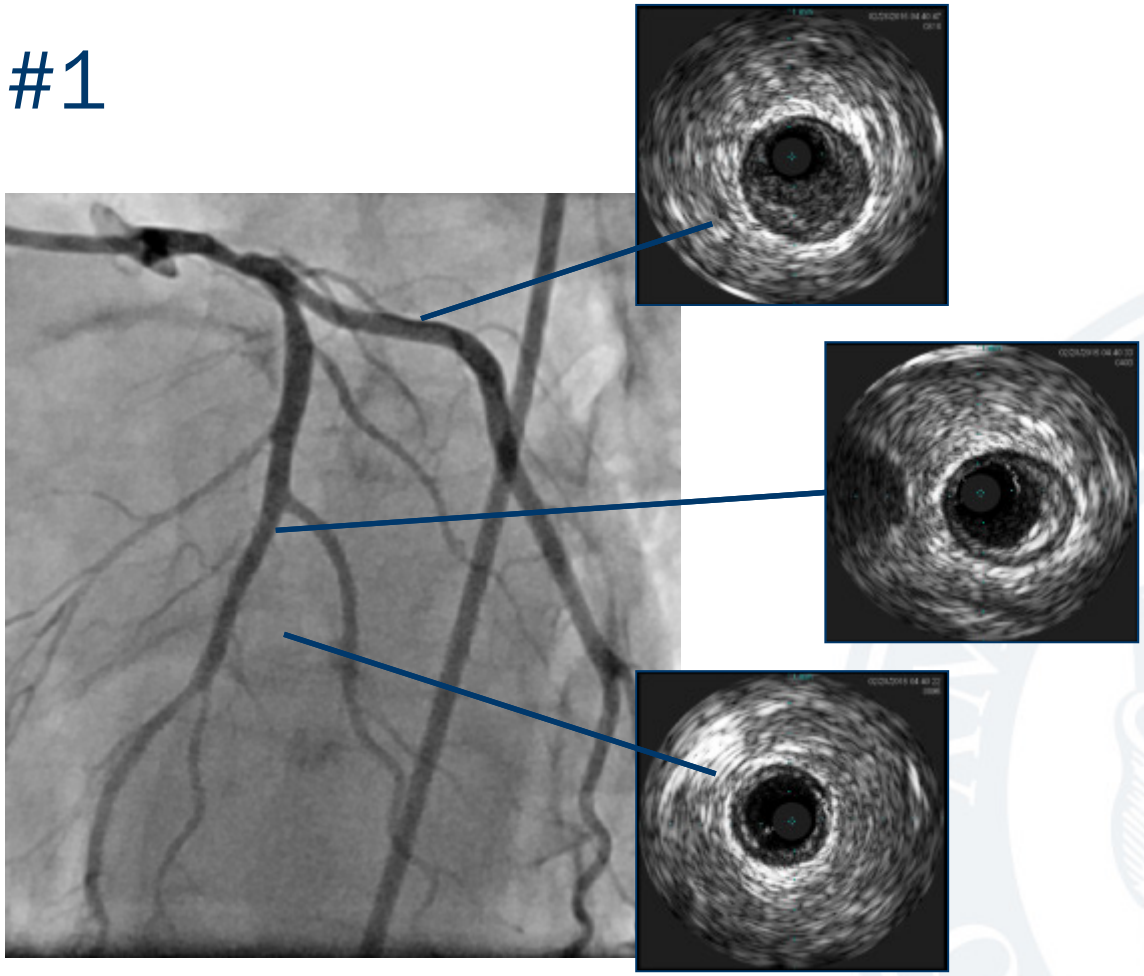
Case #1



Case #1



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Questions Raised

- Comprehensive screening?
- When and how to screen?
- How to respond to screening?
- How to follow after intervention?
- How to evaluate and pursue prevention?

Treatment Recommendations

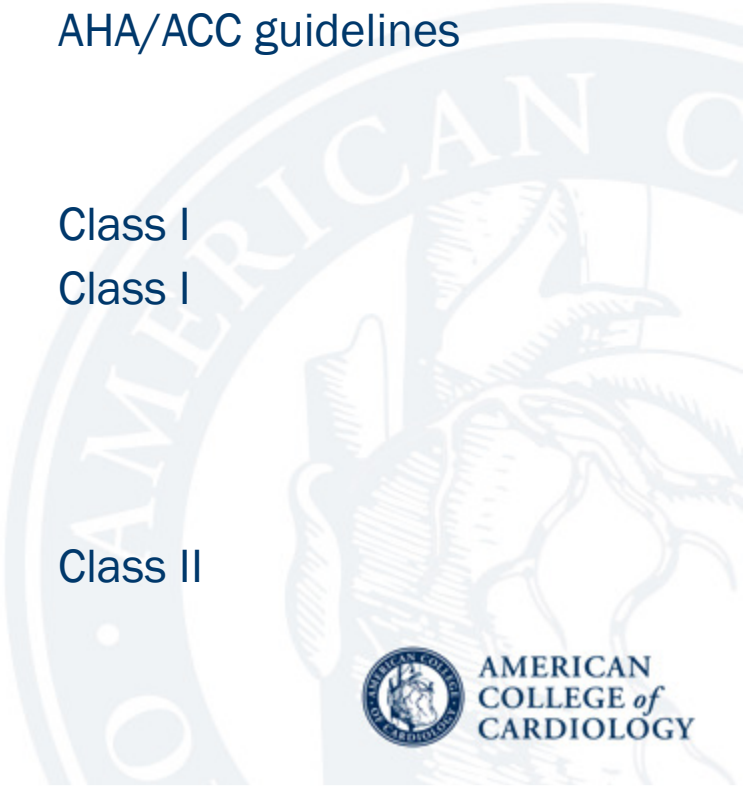
	Symptomatic Improvement	Reduced Cardiovascular Risk
Exercise	+++	Not studied
Cilostazol	++	Neutral
Statins	+/−	+++
Antiplatelets	−	+++
L-Carnitine and propionyl-L-carnitine	++	Not studied
Pentoxifylline	++	Not studied
Naftidrofuryl	++	Not studied
ACE inhibitor		++

AHA/ACC guidelines

Class I

Class I

Class II



Treatment Recommendations

	Symptomatic Improvement	Reduced Cardiovascular Risk	AHA/ACC guidelines
Exercise			
Cilostazol			
Statins			
Antiplatelets			
L-Carnitine			
propionyl-L-			
Pentoxifyllin			
Naftidrofury			
ACE inhibitor		++	Class II

Should this be done
in every patient before
the start of BCR-Abl therapy or
only in those at high risk
by risk calculators ?

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Summary: CV Toxicities of BCR-Abl TKIs

- accelerated atherosclerosis, especially Nilotinib and Ponatinib
- difficulties in cause-effect relationship determinations/ adjudication of events
- no intervention or prevention studies
- management not defined

Summary: ABI as a Universal Test

- ABIs hold promise as a prime surveillance test, but validation and role of baseline test not defined
- Role of additional testing (carotid U/S, cardiac stress test, CCTA) not defined
- Interpretation of tests in the broader scope of the disease and need for therapy

Summary: Other CV Toxicities of BCR-Abl TKIs

- systemic hypertension with ponatinib (office or ambulatory monitoring?)
- pulmonary hypertension and effusions with dasatinib (routine echocardiogram?)
- QTc prolongation with nilotinib (regular ECGs?)

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