炎性關節炎相關的共病

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講題內容

- 炎性關節炎相關的共病的簡要介紹
- 患者並發動脈粥樣硬化的發生率是否增高？
- 如何可以早期診斷？
- 有效抑制炎症，是否能防止動脈粥樣硬化的進展？
- 總結

類風濕性關節炎

- Rheumatoid Arthritis (簡稱RA)
- 自身免疫系統疾病
  - 免疫系統攻擊自身的關節
  - 引發慢性的炎性疾病
  - 以致活動能力亦可能受影響

牛皮癬關節炎

- Psoriatic arthritis (簡稱 PsA)
  - 是一種伴隨牛皮癬的慢性、炎性關節炎。
  - 此病並無傳染性。

牛皮癬的病徵

常發於頭皮及四肢外側，特別是肘和膝外側，從輕度鱗屑型到廣泛的剝脫型都可能發生。

- 約八成患者有指甲病變，如失去光澤、變濁、增厚、粗糙、頂針樣凹陷、甲下過角化、甲剝離等。

強直性脊柱炎

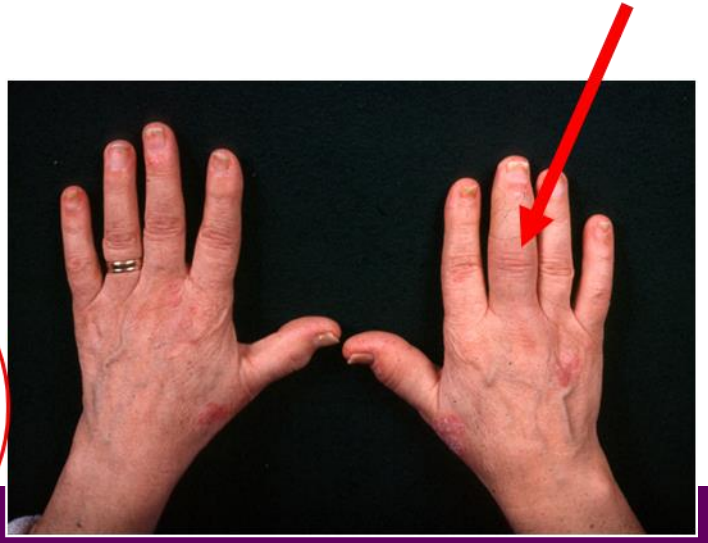
強直性脊柱炎及牛皮癬關節炎的其他病徵

- 韌帶連接骨的交着點發炎
- 指炎
- 眼睛發炎，如角膜炎、虹膜炎等。

Oligo-arthritis

Heel enthesitis

Dactylitis

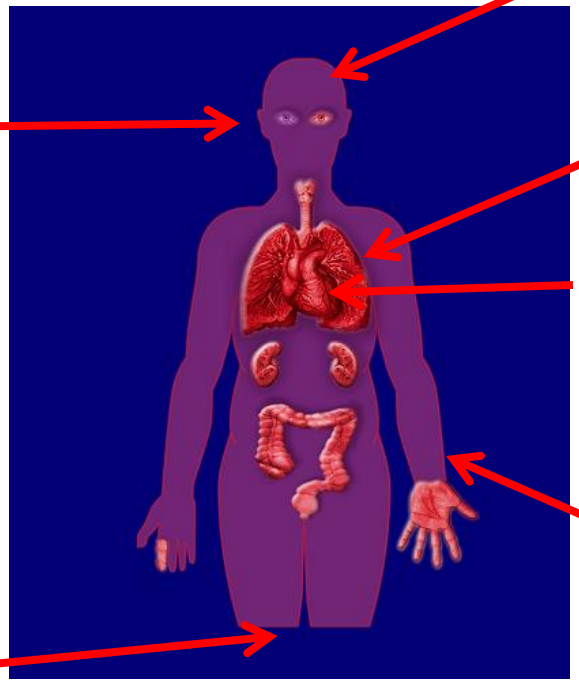


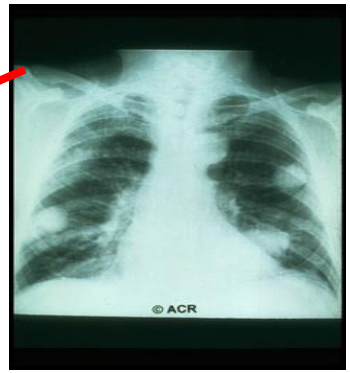
類風濕性關節炎：關節以外的其他併發症

鞏膜炎

神經炎

心包炎



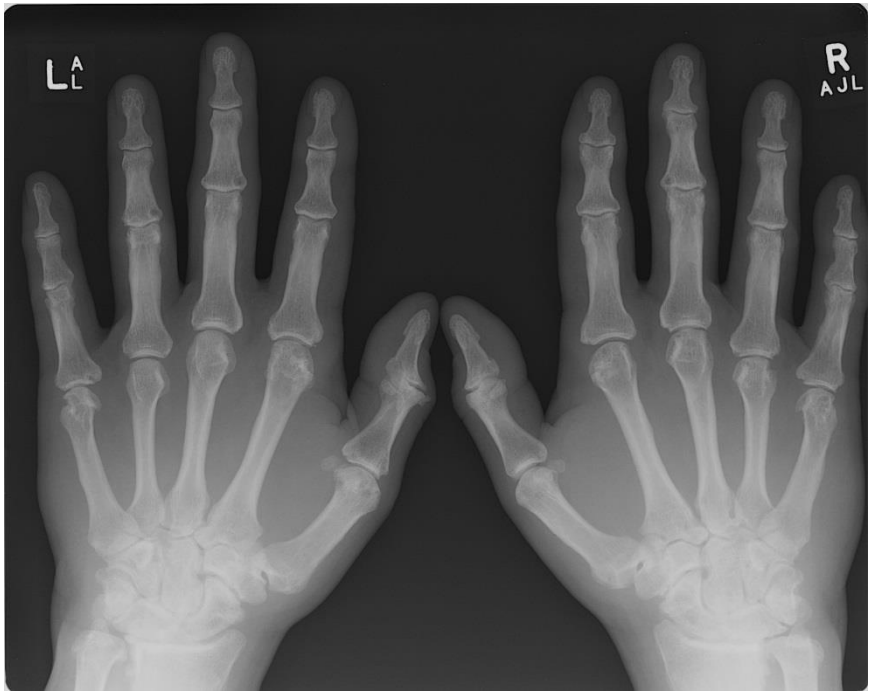


肺部疾病

風濕肉瘤

血管炎

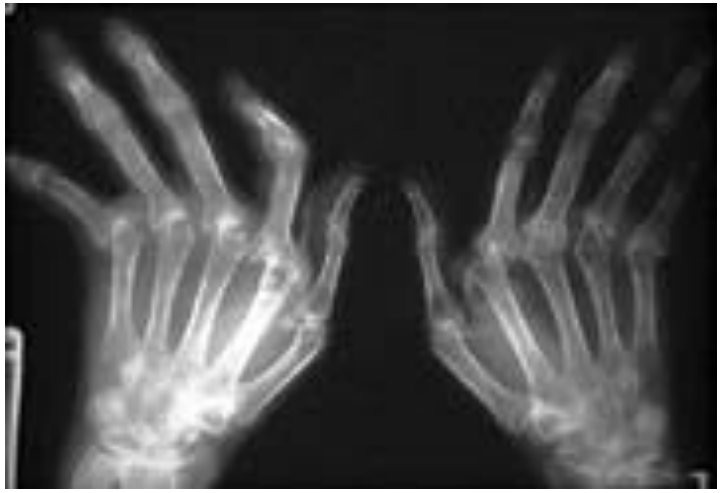
如不治理，關節炎可損壞關節組織

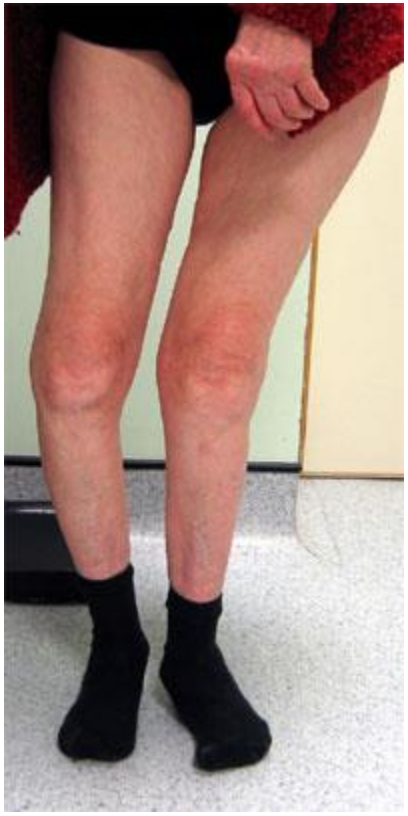


銀屑病關節炎

銀屑病關節炎患者關節變形的情況

類風濕性關節炎患者關節變形的情況



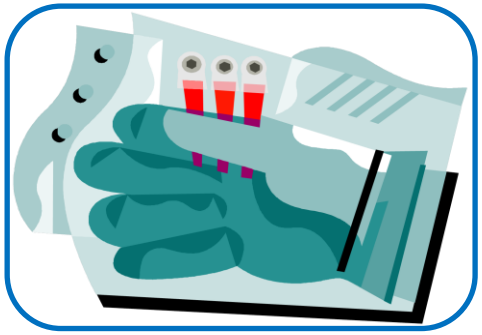


診斷方法

驗血

晨僵和關節腫痛現象

X光



RF, Anti-CCP 抗体

HLA B27

超聲波

磁力共振

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治療方案

藥物治療

傳統療法

- 一般止痛藥、痛楚調節劑
- 非類固醇抗炎藥 (NSAIDs)
- 類固醇 (Steroids)
- 改善疾病或免疫抑制藥物 (DMARDS)

治療新紀元 -近年醫學的突破

- 生物製劑

藥物治療 -改善疾病或免疫抑制藥物

- 甲氨蝶呤 methotrexate
- 柳氮磺吡啶 sulfasalazine
- 羥基氯喹 hydroxychloroquine
- 來氟米特 Leflunomide
- 金製劑 (口服、注射)
- 環孢素 cyclosporin A

生物製劑

- 抗甲型腫瘤壞死因子藥物 (Anti TNFa)
  Infliximab (因福利美), Golimumab (戈木利單抗), Adalimumab (阿達木單抗), Etanercept (依那西普), Certolizumab pegol
- 生物仿製藥 e.g. Remsima
- Secukinumab (蘇金單抗)
- Ustekinumab(烏司奴單抗)
- Tofacitinib (托法替尼)
- Apremilast

關節炎治療新目標

- 關節炎不能根治,但可控制
- 治療新目標-緩解(臨床, XR,功能維持,生活質素)
- 食藥定時,定時覆診
- 控制有關的高血壓,高膽固醇,糖尿病, 代謝綜合症

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病情活躍評分

病況評估指標

- 腫脹關節數目
- 疼痛關節數目
- 病人疼痛的嚴重程度
- 病人總體健康評估
- 醫生總體健康評估
- 驗血發炎指數: ESR (血沉降)或CRP (c-反應蛋白)
- 功能
- 生活質素
- 皮膚疾病的嚴重性
- 脊椎疾病的嚴重程度
- 韌帶連接骨的交着點發炎
- 指炎
- **關節以外的其他併發症**
- 放射診斷: X-ray

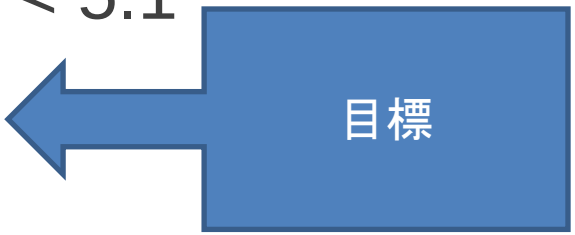
RA病況評估指標:

Disease Activity Score (病情活躍評分)28

- 腫脹關節數目
- 疼痛關節數目
- 驗血指標: ESR或CRP
- 病人總體健康評估 (Global Health)

Score Range (0 – 9.4)

- 嚴重High: >5.1
- 中度Moderate: >3.2 and < 5.1
- 輕度Low: <3.2
- 緩解Remission:<2.6



PsA Minimal disease activity (MDA) criteria
最小疾病活躍程度

- 5 of the following 7 criteria are met:
  - 疼痛關節數目≤1
  - 腫脹關節數目≤1
  - 皮膚疾病的嚴重程度PASI ≤1 or BSA ≤3
  - 病人疼痛的嚴重程度VAS ≤15
  - 病人總體健康評估VAS ≤20
  - 功能HAQ ≤0.5
  - 韌帶連接骨的交着點發炎≤1

PASI: Psoriasis Area and Severity Index; BSA: Body Surface Area; VAS: Visual Analogue Scale; HAQ: Health Assessment Questionnaire.

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Coates LC, et al. Ann Rheum Dis. 2010;69(1):48-53.

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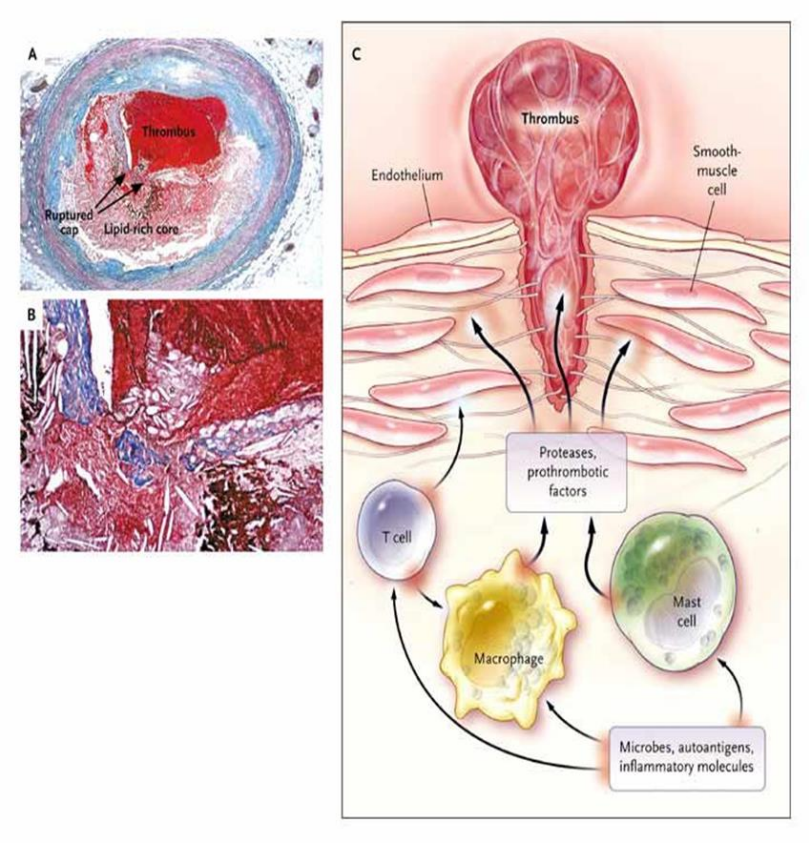
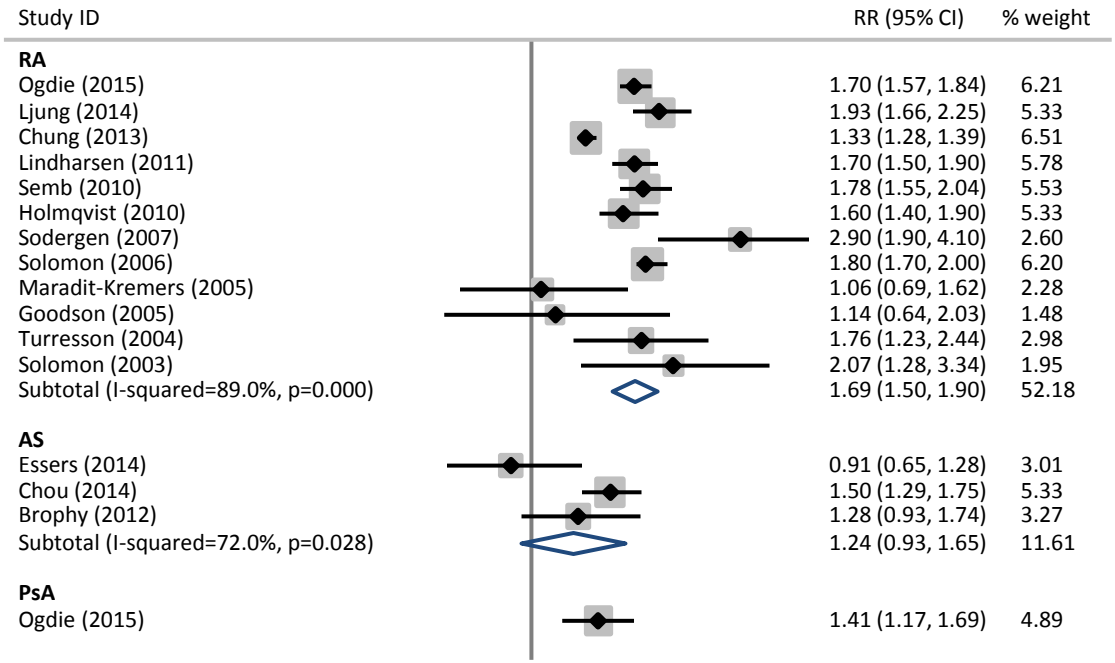
炎性關節炎與心血管疾病

動脈粥樣硬化是一種炎症！



炎症性關節炎患者心肌梗塞的風險較高



關節炎患者的心肌梗塞風險持續增加，部分原因是傳統危險因素的患病率較高

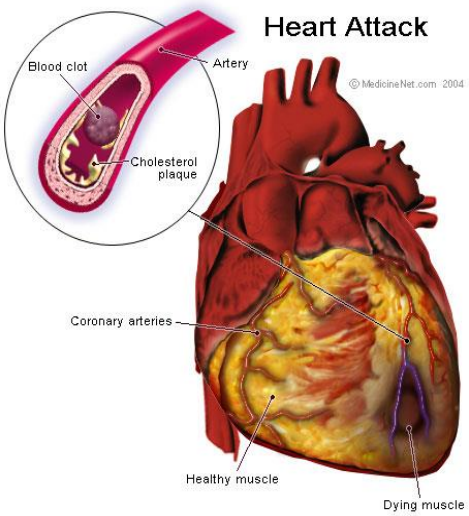
- Schieir O, et al. Ann Rheum Dis 2017;76:1396–404

關節炎並發動脈粥樣硬化的風險

- PsA標準化死亡率SMR: 1.3
- 36%的PsA患者死於心腦血管疾病

•Wong K, et al. Arthritis Rheum 1997;40:1868–72.
•Gladman DD, et al . Arthritis Rheum 1998;41:1103–10.
•Gladman DD, et al. Ann Rheum Dis 2009;68:1131-5.
•Han C, et al. J Rheumatol 2006;33:2167-72.

RA患者並發有症狀心血管損害的發生率



EXTENDED REPORT

Risk of incident cardiovascular events in patients with rheumatoid arthritis: a meta-analysis of observational studies

Juan Antonio Avina-Zubieta,[1,2] Jamie Thomas,[3] Mohsen Sadatsafavi,[4] Allen J Lehman,[1] Diane Lacaille,[1,2]

Results Fourteen studies comprising 41 490 patients met the inclusion criteria. Overall, there was a 48% increased risk of incident CVD in patients with RA (pooled RR 1.48 (95% CI 1.36 to 1.62)). The risks of MI and CVA were increased by 68% (pooled RR 1.68 (95% CI 1.40 to 2.03)) and 41% (pooled RR 1.41 (95% CI 1.14 to 1.74)).

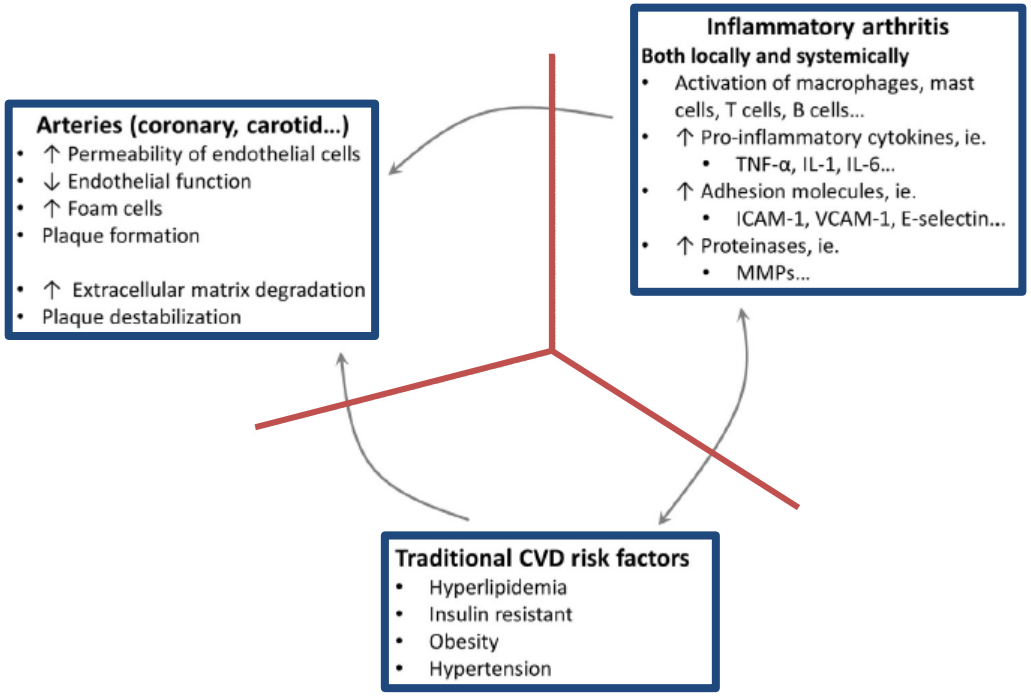
Ann Rheum Dis 2012;**71**:1524–1529. doi:10.1136/annrheumdis-2011-200726

類風濕關節炎並發動脈粥樣硬化的風險

- 標準化死亡率SMR: 4.58 (4.33–4.83)
- 19%的類風濕關節炎患者死於心腦血管疾病

CC Mok et al. ARTHRITIS & RHEUMATISM
Vol. 63, No. 5, May 2011, pp 1182–1189

炎症與傳統的心血管危險因素相互作用，加速動脈粥樣硬化



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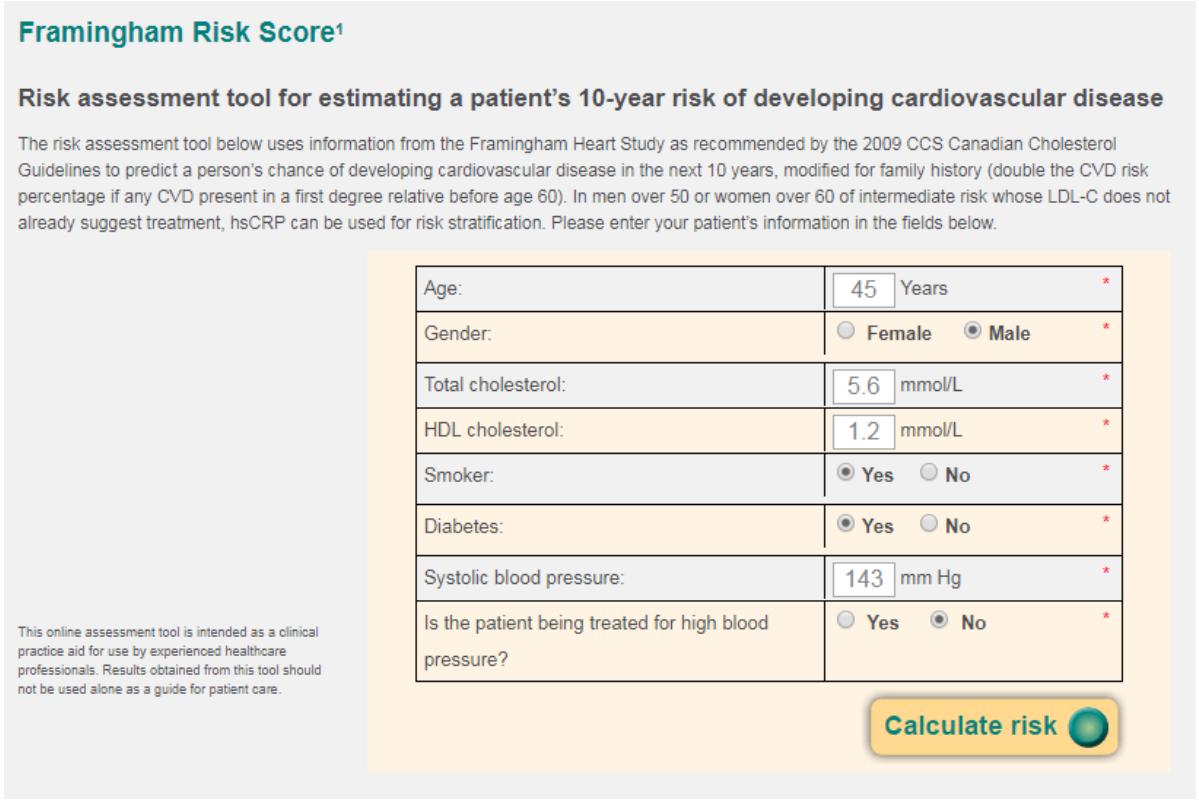
如何可以早期診斷？

您是否有增加心血管疾病的風險？
弗雷明漢風險評分



Framingham Risk Score[1]

Risk assessment tool for estimating a patient's 10-year risk of developing cardiovascular disease

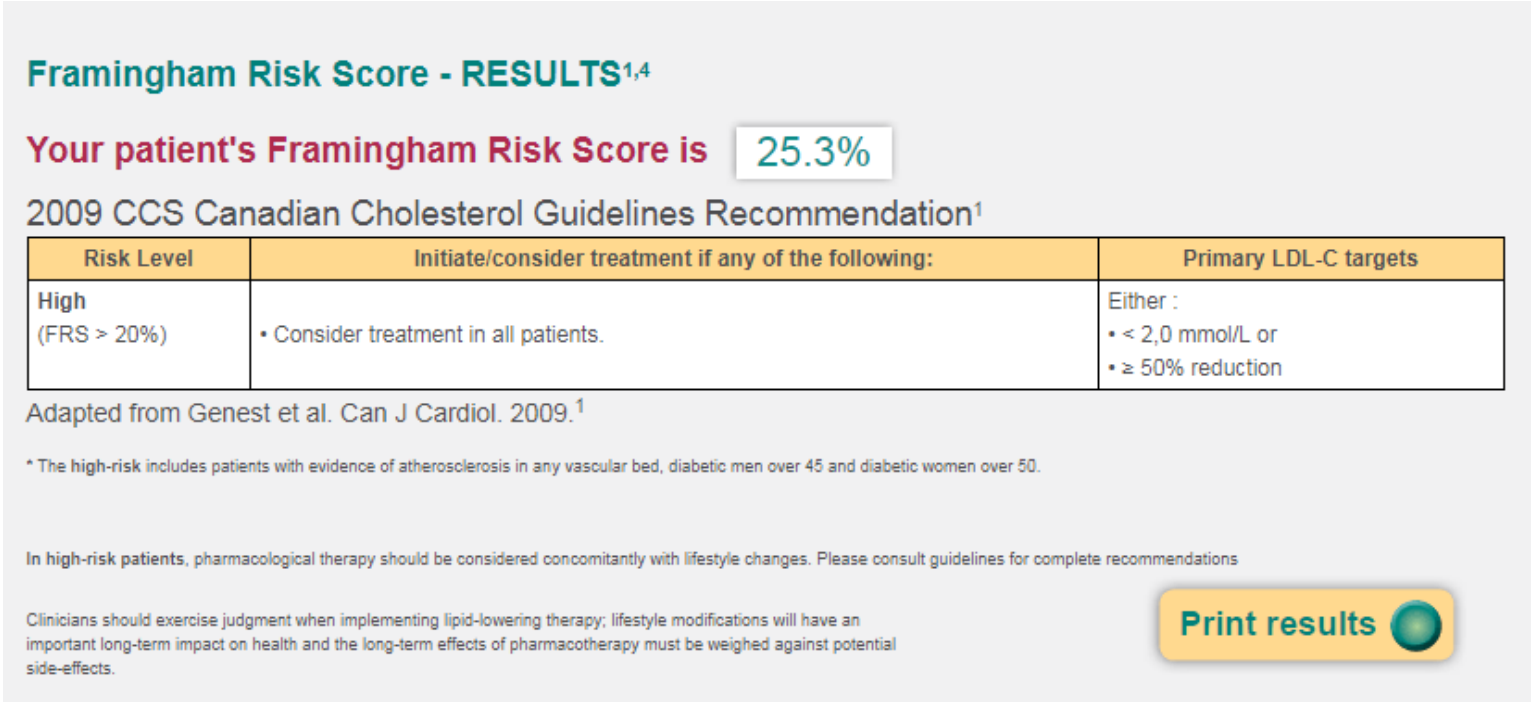
The risk assessment tool below uses information from the Framingham Heart Study as recommended by the 2009 CCS Canadian Cholesterol Guidelines to predict a person's chance of developing cardiovascular disease in the next 10 years, modified for family history (double the CVD risk percentage if any CVD present in a first degree relative before age 60). In men over 50 or women over 60 of intermediate risk whose LDL-C does not already suggest treatment, hsCRP can be used for risk stratification. Please enter your patient's information in the fields below.

Age:	45 Years *
Gender:	○ Female ◉ Male *
Total cholesterol:	5.6 mmol/L *
HDL cholesterol:	1.2 mmol/L *
Smoker:	◉ Yes ○ No *
Diabetes:	◉ Yes ○ No *
Systolic blood pressure:	143 mm Hg *
Is the patient being treated for high blood pressure?	○ Yes ◉ No *

Calculate risk

This online assessment tool is intended as a clinical practice aid for use by experienced healthcare professionals. Results obtained from this tool should not be used alone as a guide for patient care.

心血管疾病的風險高!
醫生應該建議開始服用他汀類藥物



Framingham Risk Score - RESULTS[1,4]

Your patient's Framingham Risk Score is 25.3%

2009 CCS Canadian Cholesterol Guidelines Recommendation[1]

Risk Level	Initiate/consider treatment if any of the following:	Primary LDL-C targets
High (FRS > 20%)	• Consider treatment in all patients.	Either : • < 2,0 mmol/L or • ≥ 50% reduction

Adapted from Genest et al. Can J Cardiol. 2009.[1]

* The **high-risk** includes patients with evidence of atherosclerosis in any vascular bed, diabetic men over 45 and diabetic women over 50.

In high-risk patients, pharmacological therapy should be considered concomitantly with lifestyle changes. Please consult guidelines for complete recommendations

Clinicians should exercise judgment when implementing lipid-lowering therapy; lifestyle modifications will have an important long-term impact on health and the long-term effects of pharmacotherapy must be weighed against potential side-effects.

Print results

Patient 2

Framingham Risk Score[1]

Risk assessment tool for estimating a patient's 10-year risk of developing cardiovascular disease

The risk assessment tool below uses information from the Framingham Heart Study as recommended by the 2009 CCS Canadian Cholesterol Guidelines to predict a person's chance of developing cardiovascular disease in the next 10 years, modified for family history (double the CVD risk percentage if any CVD present in a first degree relative before age 60). In men over 50 or women over 60 of intermediate risk whose LDL-C does not already suggest treatment, hsCRP can be used for risk stratification. Please enter your patient's information in the fields below.

Age:	45 Years	*
Gender:	○ Female ◉ Male	*
Total cholesterol:	3.6 mmol/L	*
HDL cholesterol:	1.2 mmol/L	*
Smoker:	◉ Yes ○ No	*
Diabetes:	○ Yes ◉ No	*
Systolic blood pressure:	136 mm Hg	*
Is the patient being treated for high blood pressure?	○ Yes ◉ No	*

Calculate risk

This online assessment tool is intended as a clinical practice aid for use by experienced healthcare professionals. Results obtained from this tool should not be used alone as a guide for patient care.

Patient 2

Framingham Risk Score - RESULTS[1,4]

Your patient's Framingham Risk Score is 9.4%

2009 CCS Canadian Cholesterol Guidelines Recommendation[1]

Risk Level	Initiate/consider treatment if any of the following:	Primary LDL-C targets
Low (FRS < 10%)	• LDL -C > 5.0 mmol/L	≥ 50% reduction

Adapted from Genest et al. Can J Cardiol. 2009.[1]

Clinical judgment should be used regarding the timing of pharmacological therapy in **low risk patients**. Please consult guidelines for complete recommendations

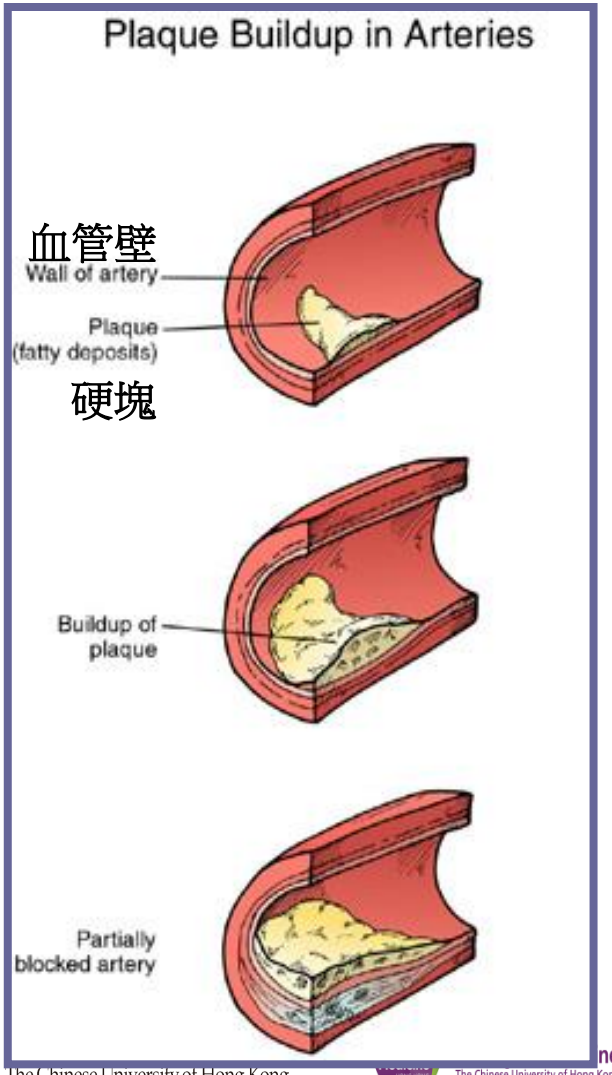
Clinicians should exercise judgment when implementing lipid-lowering therapy; lifestyle modifications will have an important long-term impact on health and the long-term effects of pharmacotherapy must be weighed against potential side-effects.

Print results

新影像技術在動脈粥樣硬化診斷上的應用

- 血管硬度測試
  - 脉搏波速度
  - 主動脈動脉擴張指數
- 頸動脈超聲波掃描
  - 血管內中膜厚度

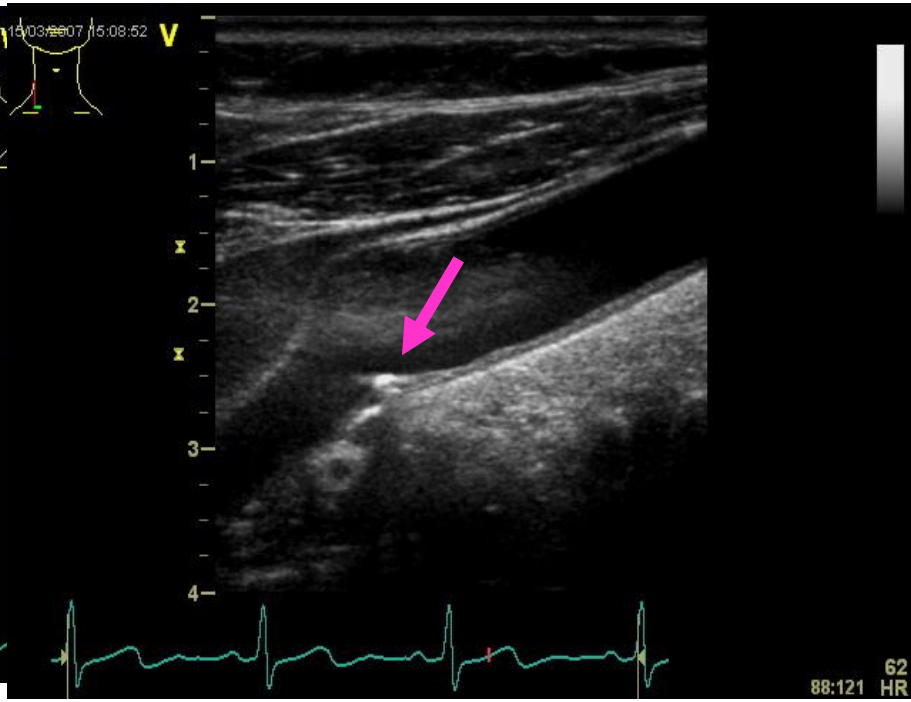
頸動脈超聲波掃描



測試頸動脈

頸動脈超聲：頸動脈管壁（IMT）增厚

健康人

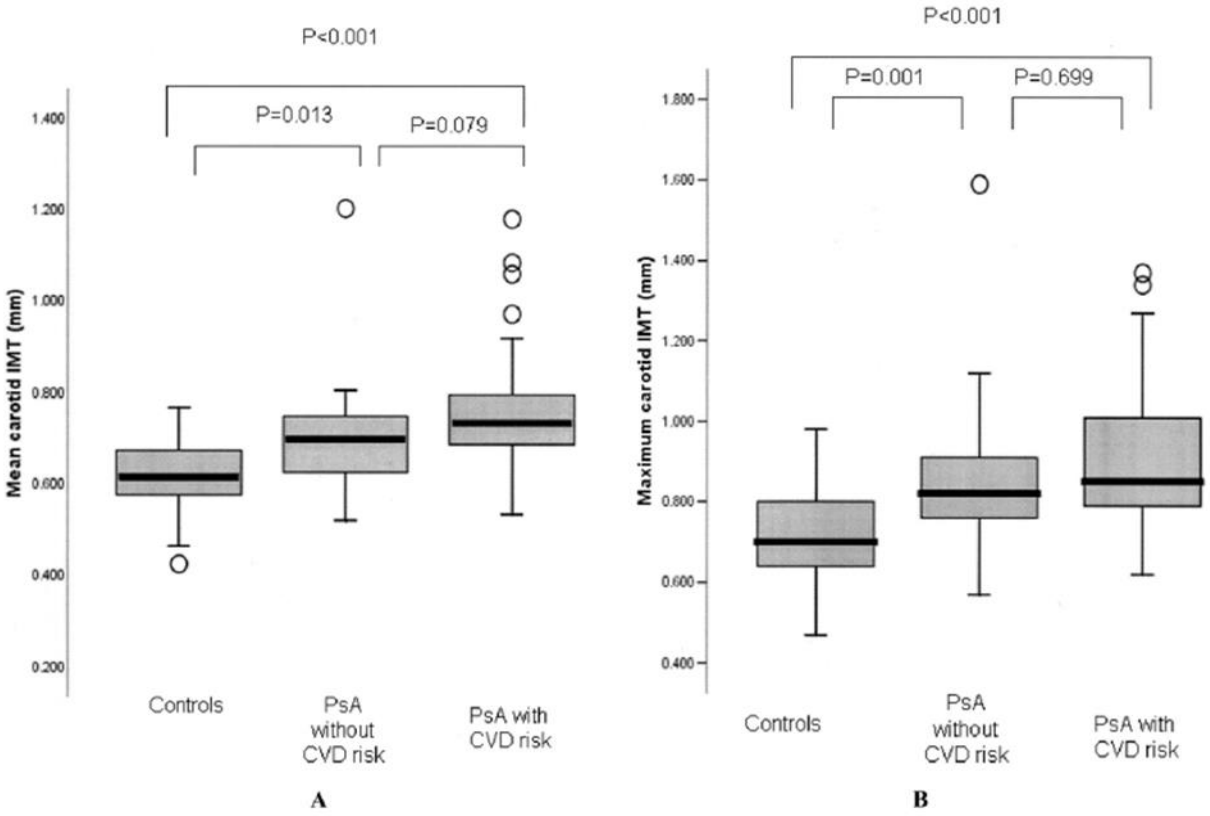


PsA患者

血管硬度測試 - 脈搏波速度
Vessel Stiffness Test - PWV

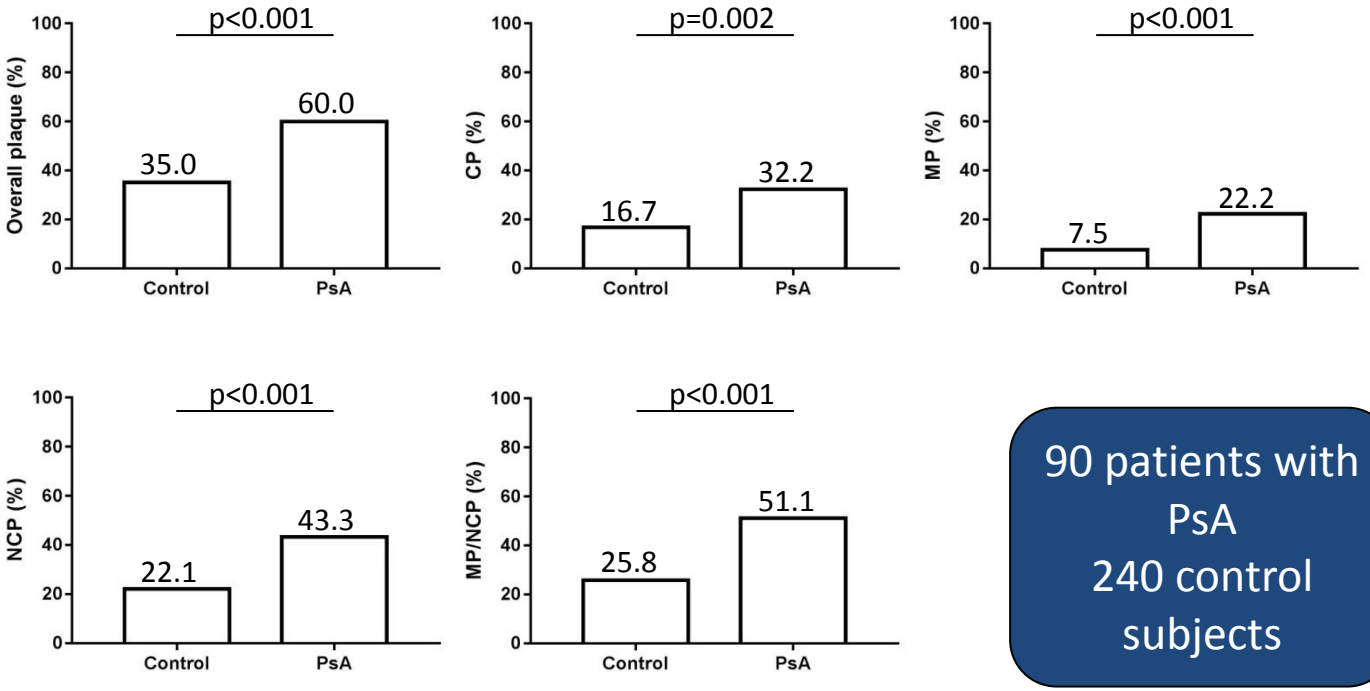
血管硬度測試 - 主動脈動脉擴張指數
Vessel Stiffness Test – Aortic AI

銀屑病關節炎患者有早期動脈粥樣硬化的病徵，因而引致心血管疾病的機會較一般人高



Tam LS, et al. Arthritis Rheum. 2008;59:1322-31.

PsA患者冠狀動脈粥樣硬化的患病率和嚴重程度較高



90 patients with PsA
240 control subjects

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- Shen J, et al. Ann Rheum Dis 2017;76:1237–44

背景

- 持續的發炎有可能是導致關節炎患者有早期血管粥樣硬化，因此，研究壓止炎症對患者預防心血管疾病，將成為值得研究的議題。

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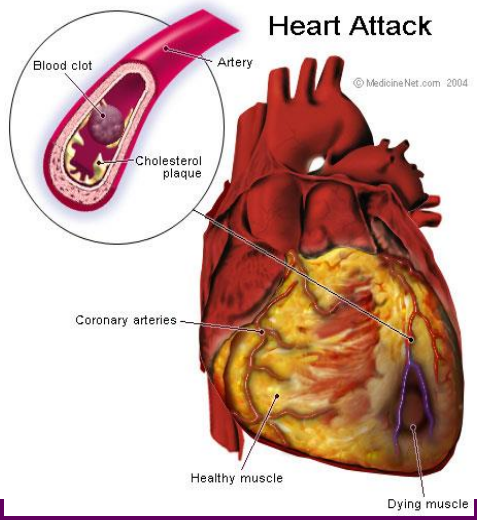
有效抑制炎症，是否能預防心血管疾病？

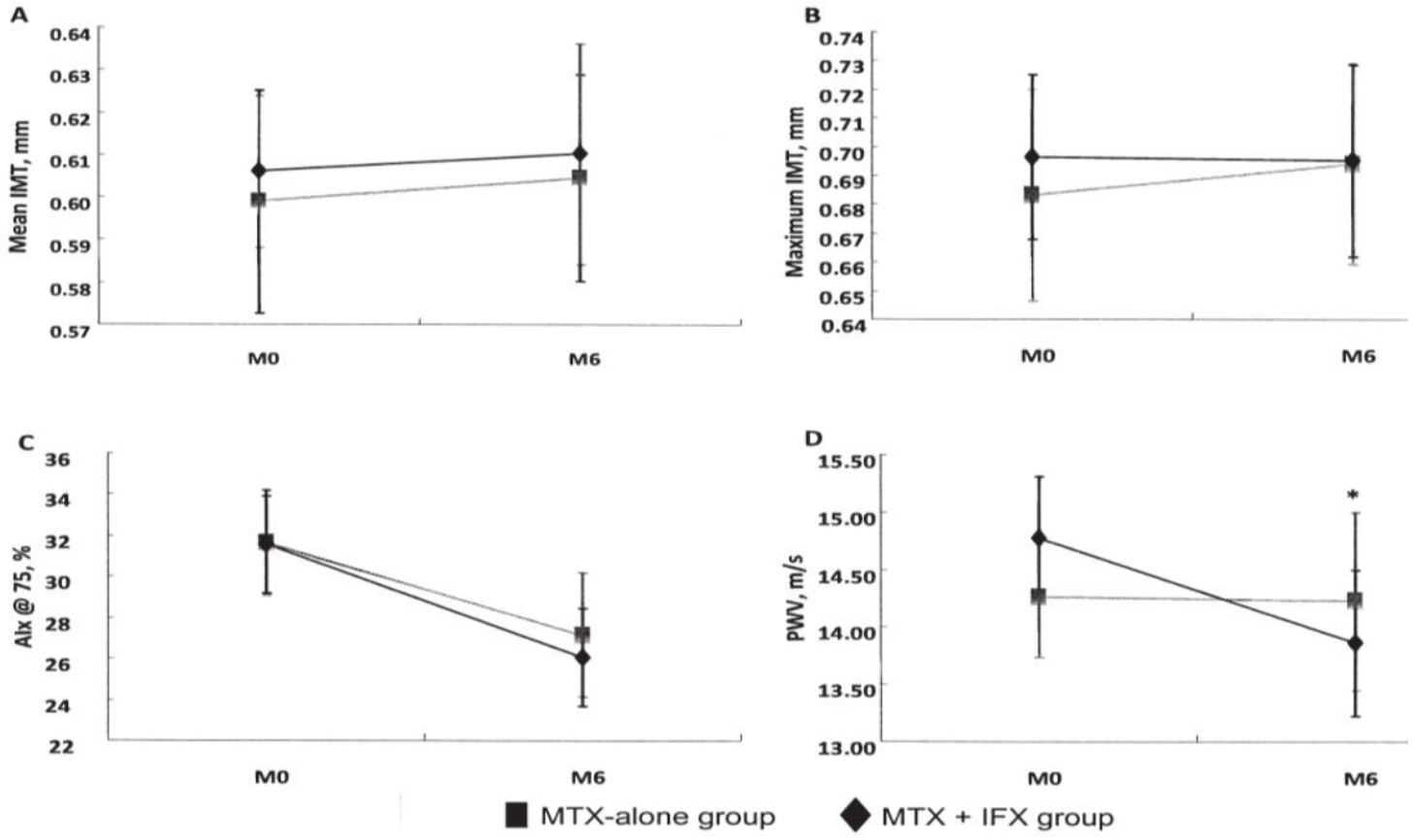
改善疾病抗風濕藥或生物製劑有效嗎？

- 未服用改善疾病抗風濕藥的PsA患者**心血管疾病**風險較高 (HR 1.24, 95% CI 1.03 to 1.49)
- 與csDMARD治療相比，接受TNFi的RA患者的MI風險降低
- 這可能歸因於TNFi對動脈粥樣硬化過程的直接作用，和/或更好的整體疾病控制



Ogdie A, et al. Ann Rheum Dis 2015;74:326–332
Low ASL, et al. Ann Rheum Dis 2017;76:654–60

抗腫瘤壞死因子生物製劑可改善早期類風濕性關節炎患者的血管硬化



抗腫瘤壞死因子生物製劑可防止強直性脊柱炎炎患者的血管硬化惡化

	Baseline	6 Month	P-value*
Mean IMT , mm			
Placebo (n=21)	0.51 ± 0.07	0.53 ± 0.08	0.044
Golimumab (n=18)	0.52 ± 0.07	0.54 ± 0.09	0.099
Maximum IMT , mm			
Placebo (n= 21)	0.54 ± 0.08	0.56 ± 0.10	0.085
Golimumab (n=19)	0.56 ± 0.09	0.56 ± 0.10	0.852
baPWV, m/s			
Placebo (n=20)	12.19 ± 1.56	12.63 ± 1.32	0.028
Golimumab (n=19)	12.41 ± 1.46	12.35 ± 1.57	0.855
Aortic AIx			
Placebo (n=20)	12.35 ± 10.3	11.60 ± 10.9	0.700
Golimumab (n=19)	11.4 ± 11.8	13.1 ± 10.9	0.454

抗腫瘤壞死因子生物製劑可改善銀屑病關節炎頸動脈超聲波內膜中層厚度增加

	Group 1	Group 2	Group 3	p-value
Mean IMT, mm				0.010#
Baseline	0.70(0.63-0.74)	0.71(0.60-0.73)	0.79(0.74-0.83)	
3 months	0.68 (0.64-0.73)	0.67(0.62-0.70) †	--	
2 years	0.63(0.59-0.75)	0.67(0.62-0.74)	0.82(0.71-0.86) †	
Maximum IMT, mm				0.013#
Baseline	0.81(0.70-0.90)	0.78(0.71-0.84)	0.90(0.81-1.15)	
3 months	0.80(0.70-0.89) †	0.74(0.70-0.79) †	--	
2 years	0.75(0.65-0.85) †	0.78(0.70-0.82)	0.87(0.82-1.12)	
Annualized rate of change, mean (95%CI) mm/year				
Mean IMT	-0.0137 (-0.0381 to 0.0106)	-0.0069 (-0.0294 to 0.0156)	0.0129 (0.0001 to 0.0257)	0.058*
Maximum IMT	-0.0223 (-0.0392 to -0.0054)	-0.0167 (-0.0487 to 0.0153)	-0.0077 (-0.0317 to 0.0163)	0.713*

Tam LS, et al. Ann Rheum Dis 2011;70:75-6.

抗腫瘤壞死因子生物製劑可改善銀屑病關節炎內膜中層厚度增加

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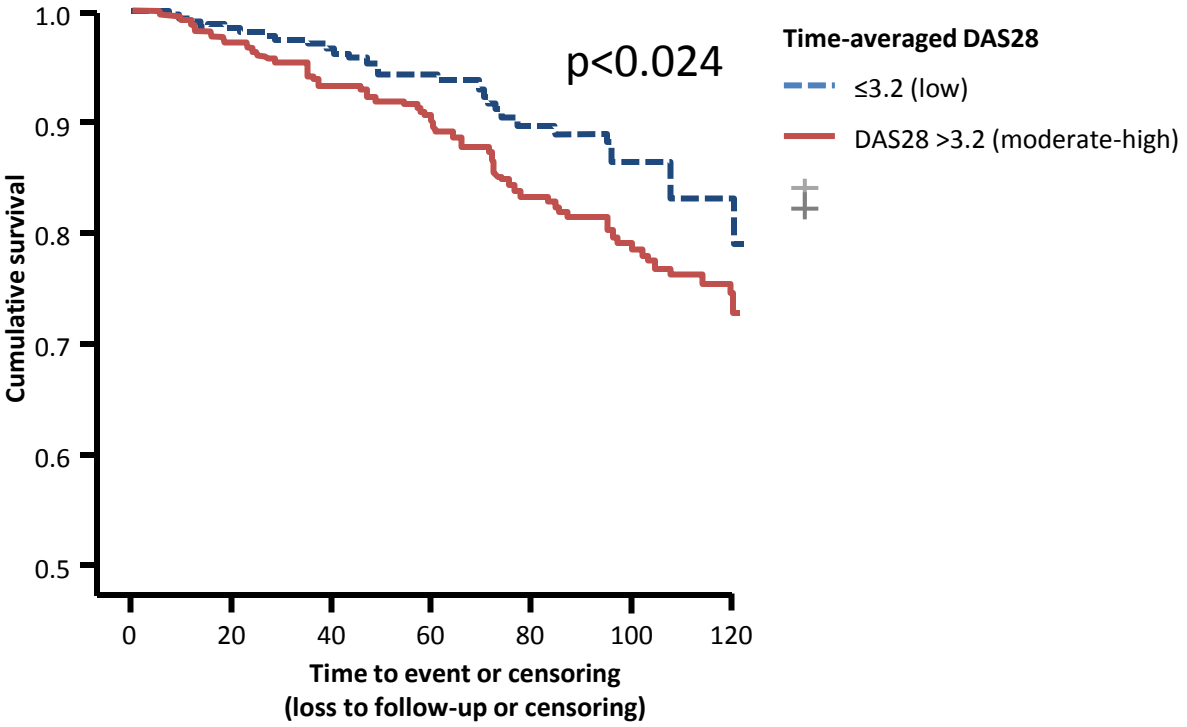
結論

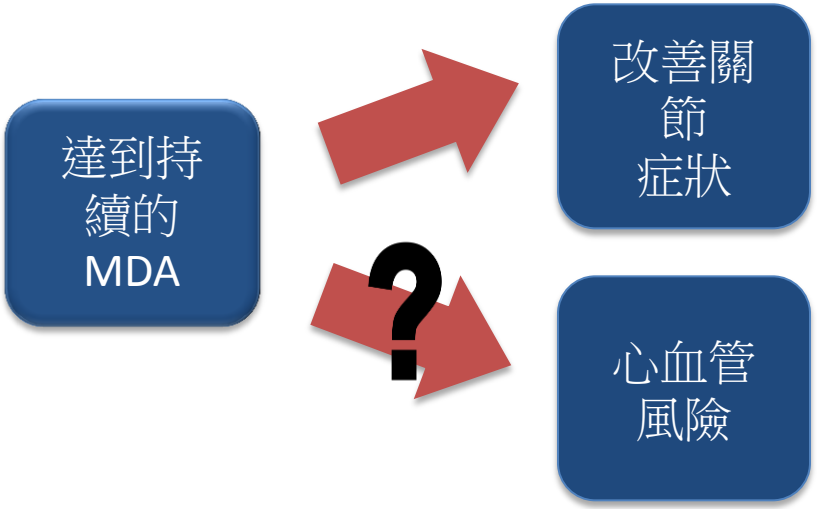
- 研究顯示，使用抗腫瘤壞死因子生物製劑有效抑制關節炎患者之炎症，並能改善其血管功能，達到預防心血管疾病的作用

低疾病活躍程度（DAS28≤3.2）降低了RA中首次發生心血管疾病的風險



Arts EEA, et al. Ann Rheum Dis 2017;76:1693–9

牛皮癬關節炎低疾病活動程度對心血管風險的影響：一項2年的前瞻性隊列研究



- MDA, minimal disease activity

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牛皮癬關節炎低疾病活動程度對心血管風險的影響：一項2年的前瞻性隊列研究

目標

- 就是對100名牛皮癬關節炎患者進行為期2年的觀察
- 比較在2年後，在能夠達到低疾病活動程度（minimal disease activity）和不能夠達到低疾病活動程度的患者之間，比較他們頸動脈內膜中層厚度和動脈硬化的變化，從而探討低疾病活動程度作為牛皮癬關節炎的治療目標，除了能夠改善關節炎以外，是否也能夠有效降低患者的心血管風險。

達到持續的MDA能夠預防頸動脈粥樣硬化

	Univariate analysis			Multi-variate analysis[a]		
	OR	95% CI	p-value	OR	95% CI	p-value
Age	1.040	0.996–1.085	0.073	1.069	1.009–1.131	0.023
Gender	1.133	0.479–2.680	0.777			
Baseline deformed joint count	0.886	0.801–0.981	0.020			
Baseline VAS Physician Global	0.980	0.960–1.001	0.062	0.964	0.936–0.993	0.016
Baseline plasma TC	1.958	1.173–3.266	0.010			
Baseline plasma LDL-c	2.226	1.200–4.129	0.011	2.628	1.310–5.493	0.007
Baseline plasma total triglyceride	1.529	0.919–2.545	0.102	1.856	0.974–3.539	0.060
bDMARD use at baseline	0.298	0.078–1.137	0.076	0.110	0.018–0.652	0.015
Presence of carotid plaque, baseline	2.222	0.914–5.404	0.078			
Sustained MDA	0.508	0.211–1.221	0.130	0.273	0.088–0.846	0.024

- [a]Adjusted for age, gender, baseline deformed joint count, NRS physician global score, total triglyceride, TC, LDL-c level, use of bDMARDs, and presence of carotid plaque at baseline
bDMARD, biologic disease-modifying anti-rheumatic drug; OR, odds ratio; VAS, visual analog scale

- Cheng I, et al. Arthritis Rheumatol 2018, in press

降膽固醇藥物對患有炎症性關節病的患者同樣有效預防心血管疾病嗎？

- 18 889名患者參加了兩項臨床試驗
- RA：199
- AS：46
- PsA：35
- 阿托伐他汀80 mg或常規/低劑量阿托伐他汀10 mg或辛伐他汀20-40 mg
- 5年

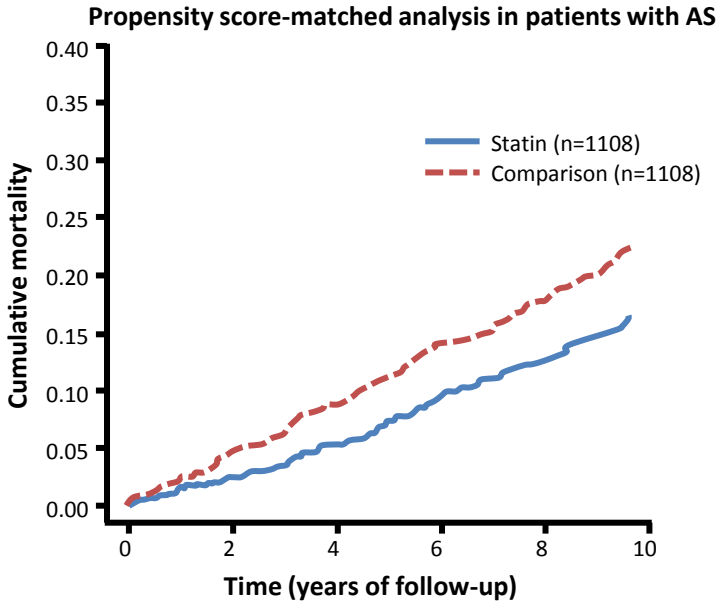
與低劑量他汀類藥物治療相比，阿托伐他汀80 mg治療導致脂質水平相當，心血管疾病總體風險降低20%，炎症性關節病的患者和無炎症性關節病的患者同樣有效

- [a]The effect of treatment on CVD risk was similar in patients with IJD and those without IJD, although the risk reduction in patients with IJD was not significant

Semb AG, et al. Arthritis Rheum 2012;64:2836–46

AS患者使用他汀類藥物可使死亡風險降低37%

Association between statin initiation and all-cause mortality (propensity score-matched cohort)		
	Statin initiator (n=1108)	Non-initiator (n=1108)
Mean follow-up, PYs	5.3	5.1
Deaths, n	96	134
Mortality rate/1000 PYs (95% CI)	16.51 (13.37 to 20.16)	23.79 (19.93 to 28.17)
HR (95% CI)	0.63 (0.46 to 0.85)	1.00 (Ref)
Rate difference/1000 PYs (95% CI)	–7.3 (–12.5 to –2.1)	0.0 (Ref)



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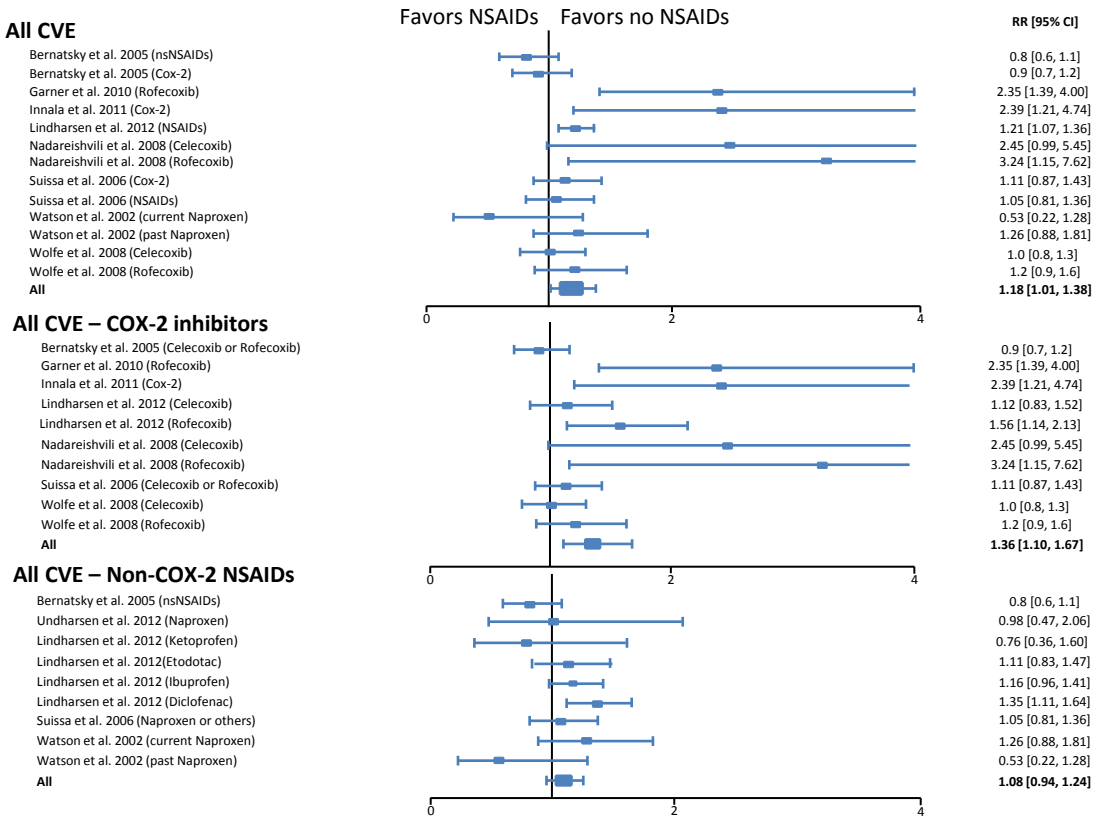
Oza A, et al. Ann Rheum Dis 2017;76:1737–42

NSAIDs增加RA，銀屑病和PsA的心血管疾病風險：Meta分析 臨床試驗



這主要是由於已經退出市場的rofacoxib的影響

總結

- 炎症性關節患者有並發早發動脈粥樣硬化的風險增高
- 系統性的炎症反應，與其他代謝危險因素相互作用，導致動脈粥樣硬化的發生及其進展
- 疾病特異性的機制也有可能進一步引發動脈粥樣硬化
- 早期診斷，再配合強化的抗炎症以及其他心血管危險因素的治療，可能對降低風險有重要作用

THANK YOU!

謝謝！

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答問時間