Rheumatologie und Kardiologie – bei Rheuma leidet häufig auch das Herz

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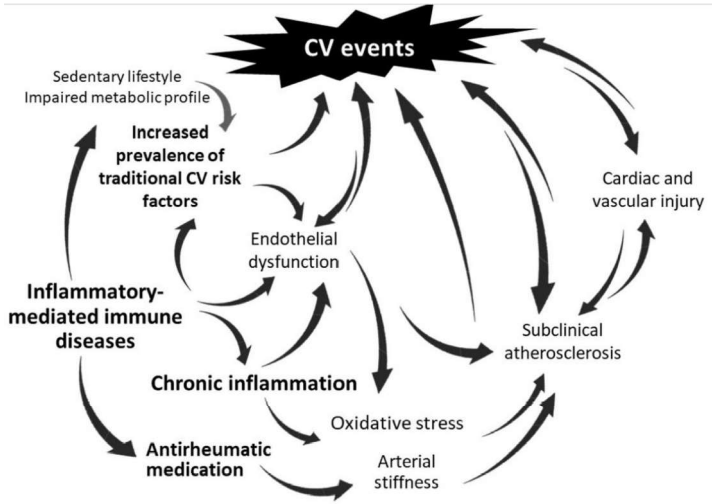
Agenda

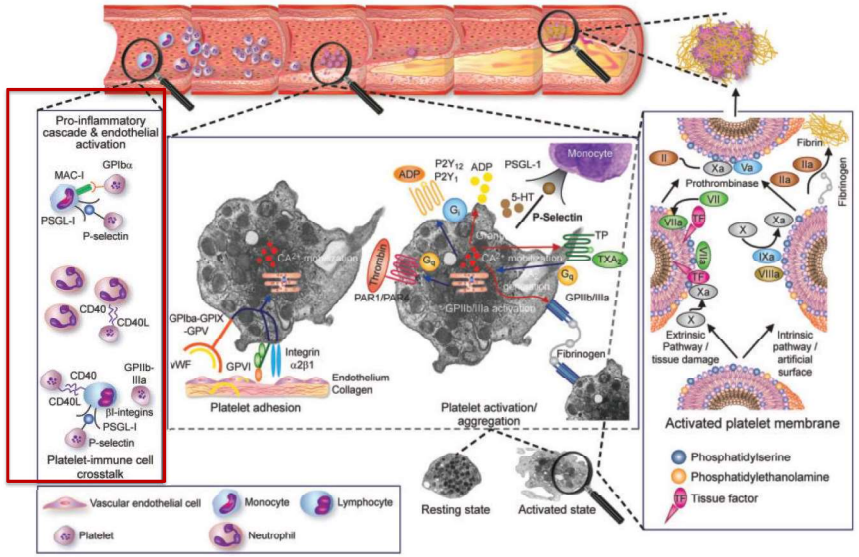
- Assoziation zwischen chron. entzündlichen und kardialen Erkrankungen
- NSAR und Herz – COX1, COX2 oder was?
- Fallbeispiele
  - Herzinsuffizienz, KHK, Vorhofflimmern
- Fazit

Factors implicated in the pathogenesis of increased cardiovascular disease (CVD) risk in patients with immune-mediated inflammatory diseases.



Journal of Inflammation Research 2021:14 6893–6906

Atherothrombose und chronische Entzündung



Beer HJ, Bonetti M. Eur Heart J 2017

The NEW ENGLAND JOURNAL of MEDICINE

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Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

P.M. Ridker, B.M. Everett, T. Thuren, J.G. MacFadyen, W.H. Chang, C. Ballantyne, F. Fonseca, J. Nicolau, S.D. Anker, J.J.P. Kastelein, J.H. Cornel, P. Pais, D. Pella, J. Genest, R. Cifkova, A. Lorenzatti, T. Forster, L. Vida-Simiti, M. Flather, H. Shimokawa, H. Ogawa, M. Dellborg, P.R.F. Rossi, R.P.T. Troquay, P. and R.J. Glynn, for the CANTOS Trial Group*

ABSTRACT

BACKGROUND

Experimental and clinical data suggest that reducing inflammation without affecting lipid levels may reduce the risk of cardiovascular disease. Yet, the inflammatory hypothesis of atherothrombosis has remained unproved.

METHODS

We conducted a randomized, double-blind trial of canakinumab, a therapeutic monoclonal antibody targeting interleukin-1β, involving 10,061 patients with previous myocardial infarction and a high-sensitivity C-reactive protein level of 2 mg or more per liter. The trial compared three doses of canakinumab (50 mg, 150 mg, and 300 mg, administered subcutaneously every 3 months) with placebo. The primary efficacy end point was nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death.

RESULTS

At 48 months, the median reduction from baseline in the high-sensitivity C-reactive protein level was 26 percentage points greater in the group that received the 50-mg dose of canakinumab, 37 percentage points greater in the 150-mg group, and 41 percentage points greater in the 300-mg group than in the placebo group. Canakinumab did not reduce lipid levels from baseline. At a median follow-up of 3.7 years, the incidence rate for the primary end point was 4.50 events per 100 person-years in the placebo group, 4.11 events per 100 person-years in the 50-mg group, 3.86 events per 100 person-years in the 150-mg group, and 3.90 events per 100 person-years in the 300-mg group. The hazard ratios as compared with placebo were as follows: in the 50-mg group, 0.93 (95% confidence interval [CI], 0.80 to 1.07; P=0.30); in the 150-mg group, 0.85 (95% CI, 0.74 to 0.98; P=0.021); and in the 300-mg group, 0.86 (95% CI, 0.75 to 0.99; P=0.031). The 150-mg dose, but not the other doses, met the prespecified multiplicity-adjusted threshold for statistical significance for the primary end point and the secondary end point that additionally included hospitalization for unstable angina that led to urgent revascularization (hazard ratio vs. placebo, 0.83; 95% CI, 0.73 to 0.95; P=0.005). Canakinumab was associated with a higher incidence of fatal infection than was placebo. There was no significant difference in all-cause mortality (hazard ratio for all canakinumab doses vs. placebo, 0.94; 95% CI, 0.83 to 1.06; P=0.31).

CONCLUSIONS

Antiinflammatory therapy targeting the interleukin-1β innate immunity pathway with canakinumab at a dose of 150 mg every 3 months led to a significantly lower rate of recurrent cardiovascular events than placebo, independent of lipid-level lowering. (Funded by Novartis; CANTOS ClinicalTrials.gov number, NCT01327846.)

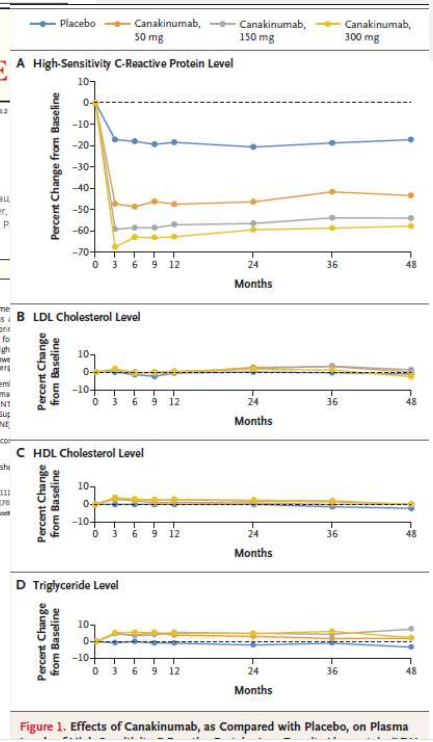

Figure 1. Effects of Canakinumab, as Compared with Placebo, on Plasma

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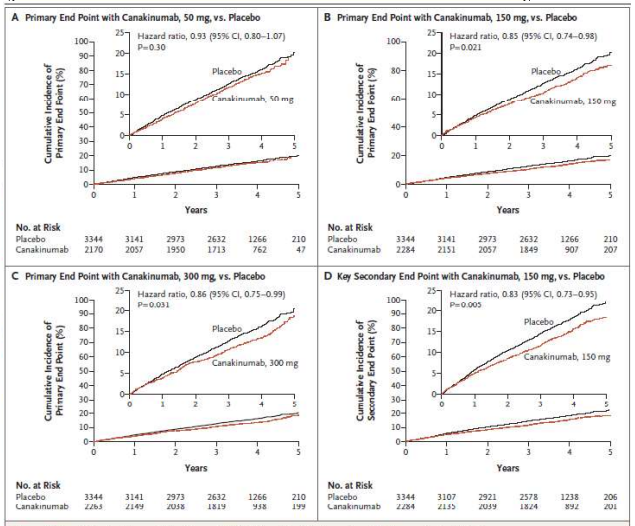


Figure 2. Cumulative Incidence of the Primary End Point and the Key Secondary Cardiovascular End Point.

Shown is the cumulative incidence of the primary end point of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death in the placebo group versus the various canakinumab dose groups (Panels A through C). The insets show the same data on an enlarged y axis. The threshold P value for the primary end point was 0.02115 in the 150-mg group and 0.01058 in the 300-mg group. The group receiving the 150-mg dose of canakinumab met the prespecified multiplicity-adjusted threshold for statistical significance for the primary cardiovascular end point and for the key secondary cardiovascular end point that additionally included hospitalization for unstable angina that led to urgent revascularization (Panel D). The threshold P value for the key secondary cardiovascular end point in the 150-mg group was 0.00529.

Table 1 | Overview of selected clinical studies targeting inflammatory pathways in cardiovascular disease

Trial	Study population	Study design	Outcome	Ref.
ASSAIL-MI	First-time STEMI presenting within 6 h of the onset of chest pain	Single dose of tocilizumab (IL-6 antibody) vs placebo	Improved myocardial salvage in patients assigned to tocilizumab	NCT03004703
CANTOS	Stable CAD, persistent elevation of hsCRP (>2 mg/l)	Canakinumab (IL-1β antibody) subcutaneously vs placebo	Canakinumab lowered plasma CRP, IL-1 and IL-6 Reduction in cardiovascular events, cancer and gout attacks Small increase in fatal infections	NCT01327846 (REF.[5])
CIRT	Stable CAD and persistent evidence of inflammation, type 2 diabetes or metabolic syndrome	Low-dose (15–20 mg) methotrexate (a purine metabolism inhibitor) once per week vs placebo	Halted prematurely for futility No change in plasma IL-1β, IL-6 and hsCRP No reduction in cardiovascular events	NCT02576067 (REF.[93])
COLCOT	Recent myocardial infarction (<30 days)	Low-dose (0.5 mg/day) colchicine (a tubulin disrupter) vs placebo	Reduction in cardiovascular death and cardiovascular events Increase in pneumonia	NCT02551094 (REF.[7])
CLEAR-Synergy	STEMI with primary PCI	SYNERGY bioabsorbable polymer drug eluting stent plus colchicine and spironolactone or placebo	Ongoing, estimated completion in early 2025	NCT03048825
CONVINCE	Adults >40 years of age with an ischaemic stroke or TIA not caused by cardiac embolism	Low-dose (0.5 mg/day) colchicine plus usual care or standard care alone	Ongoing, estimated completion in autumn 2021	NCT02898610
LATITUDE-TIMI 60	Patients hospitalized with acute myocardial infarction	Losmapimod (a selective inhibitor of p38α/β mitogen-activated protein kinases) twice per day vs placebo	No reduction in major ischaemic cardiovascular events	NCT02145468 (REF.[94])
LoDoCo	Stable CAD	Low-dose (0.5 mg/day) colchicine plus usual care or standard care alone	Significant reduction in ACS	[94]
LoDoCo2	Chronic coronary disease	Low-dose (0.5 mg/day) colchicine plus usual care or standard care plus placebo	Reduction in cardiovascular events	ACTRN12614000093684 (REF.[8])
LILACS	Stable ischaemic heart disease and ACS	Low-dose IL-2 ($0.3–3 \times 10^6$ IU/day)	Phase I/II ongoing	NCT03113773
FUTURE 1	Psoriatic arthritis (prospective randomized)	Secukinumab (IL-17A antibody) vs placebo	Improved arthritis score Increase in infections Non-significant increase in MACE	NCT01392326 (REF.[95])
Tocilizumab in NSTEMI	NSTEMI	Single dose of tocilizumab (IL-6 receptor antibody) vs placebo	Reduction in hsCRP and troponin T release	NCT01491074 (REF.[96])

ACS, acute coronary syndromes; CAD, coronary artery disease; CANTOS, Canakinumab Anti-inflammatory Thrombosis Outcomes Study; CIRT, Cardiovascular Inflammation Reduction Trial; COLCOT, Colchicine Cardiovascular Outcomes Trial; CRP, C-reactive protein; hsCRP, CRP measured with a highly sensitive assay; MACE, major adverse cardiac event; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; TIA, transient ischaemic attack.

Targeting inflammation in atherosclerosis — from experimental insights to the clinic Nature Reviews 2021

Targeting inflammation in atherosclerosis — from experimental insights to the clinic. Nature Reviews 2021

Oliver Soehnlein[1,2,3] ✉ *and Peter Libby*[4]

Abstract | Atherosclerosis, a dominant and growing cause of death and disability worldwide, involves inflammation from its inception to the emergence of complications. Targeting inflammatory pathways could therefore provide a promising new avenue to prevent and treat atherosclerosis. Indeed, clinical studies have now demonstrated unequivocally that modulation of inflammation can forestall the clinical complications of atherosclerosis. This progress pinpoints the need for preclinical investigations to refine strategies for combatting inflammation in the human disease. In this Review, we consider a gamut of attractive possibilities for modifying inflammation in atherosclerosis, including targeting pivotal inflammatory pathways such as the inflammasomes, inhibiting cytokines, manipulating adaptive immunity and promoting pro-resolution mechanisms. Along with lifestyle measures, pharmacological interventions to mute inflammation could complement traditional targets, such as lipids and hypertension, to make new inroads into the management of atherosclerotic risk.

Risks and Benefits of Janus Kinase Inhibitors in Rheumatoid Arthritis — Past, Present, and Future

Jasvinder A. Singh, M.B., B.S., M.P.H.

The Food and Drug Administration (FDA) mandated a safety study to be performed because of possible safety signals detected for the Janus kinase (JAK) inhibitor tofacitinib. As Ytterberg et al. report in this issue of the *Journal*, the Oral Rheumatoid Arthritis Trial (ORAL) Surveillance was a 4-year randomized, open-label, noninferiority, postauthorization, safety end-point trial, in which patients with active rheumatoid arthritis despite methotrexate treatment who were 50 years of age or older and had at least one additional cardiovascular risk factor were randomly assigned in a 1:1:1 ratio to receive oral tofacitinib at a dose of 5 or 10 mg twice daily or a subcutaneous tumor necrosis factor (TNF) inhibitor (etanercept or adalimumab).[1]

The risks of major adverse cardiovascular events (MACE) and cancers (excluding nonmelanoma skin cancer [NMSC]) were higher with the combined tofacitinib doses than with a TNF inhibitor, and the noninferiority of tofacitinib was not shown, with hazard ratios of 1.33 (95% confidence interval [CI], 0.91 to 1.94) for MACE and 1.48 (95% CI, 1.04 to 2.09) for cancers. The researchers estimated that during 5 years of treatment, 113 and 55 patients would need to be treated with tofacitinib at a dose of 5 mg twice daily rather than with a TNF inhibitor to result in one additional MACE and cancer, respectively. Efficacy was similar in all three trial groups with respect to multiple patient-centered and clinical outcomes.

What do these results mean? Rheumatoid arthritis is associated with an increased risk of MACE.[2] The use of TNF inhibitors[3] and other traditional and biologic disease-modifying antirheumatic drugs (DMARDs)[4] to treat rheumatoid arthritis is associated with a reduced risk of MACE, presumably through a reduction in inflammation. The most relevant estimates for MACE

rates were 1.42, 1.21, and 1.82 (with tocilizumab) per 100 person-years, respectively. The incidence rates of MACE in ORAL Surveillance were 0.91, 1.05, and 0.73 per 100 patient-years with tofacitinib at a dose of 5 mg twice daily, tofacitinib at a dose of 10 mg twice daily, and a TNF inhibitor, respectively.

ORAL Surveillance showed higher risks of MACE and cancer with tofacitinib than with a TNF inhibitor. This is a cause for concern and caution with its current and future use to treat rheumatoid arthritis. To my knowledge, no clear mechanism of action is evident or proven currently for this safety signal. Some of the difference in MACE risk between tofacitinib and a TNF inhibitor in ORAL Surveillance may be due at least partially to a greater reduction in cardiovascular risk with a TNF inhibitor than with tofacitinib. The nonuse of conventional DMARDs in this trial prevents an assessment of this hypothesis. Whether the excess MACE risk associated with the choice of tofacitinib over the choice of a TNF inhibitor is attributed to the fact that a TNF inhibitor reduced the risk of MACE relative to tofacitinib or whether tofacitinib increased the risk of MACE (i.e., as compared with placebo) cannot be determined from this trial; however, it does not change the risk–benefit analysis in choosing between the two drugs with regard to the risk of MACE.

Rheumatoid arthritis increases the risk of cancer.[8] The difference in cancer risk between tofacitinib and a TNF inhibitor in ORAL Surveillance is more difficult to understand. Cancer is listed as a black-box label warning for TNF inhibitors. The use of TNF inhibitors to treat rheumatoid arthritis may be associated with a slightly increased risk of NMSC or melanoma[9] but is not associated with an overall increase in cancer risk.[10] The trial indicates that this risk is higher with tofacitinib than with a TNF inhibitor. This finding makes tofacitinib a nonpreferred drug for patients with rheumatoid arthritis with current or previous cancer or those at risk for cancers.

What are the clinical implications of these findings? Recently, the FDA issued the black-box warning not just for tofacitinib but also for upadacitinib and baricitinib, the two other JAK inhibitors for which increased risks of MACE and cancer are considered to be class effects. The FDA also changed the indications for tofacitinib and upadacitinib from incomplete response to methotrexate to incomplete response to a TNF inhibitor. In patients with rheumatoid arthritis who have an incomplete response to methotrexate and have active disease, a TNF inhibitor will be preferred to tofacitinib for a new start, especially in persons 65 years of age or older. If patients strongly prefer or are only willing to take an oral DMARD and if the patient is 50 to 64 years of age, a detailed patient–provider discussion of the risks associated with tofacitinib as compared with TNF inhibitors and shared decision making are needed before choosing tofacitinib as the treatment option. JAK inhibitors are among important oral treatment options for rheumatoid arthritis.

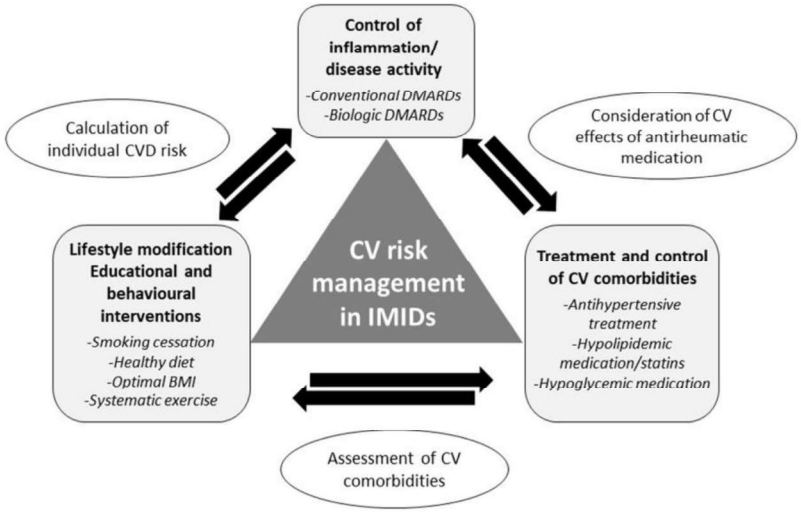
To whom do these results not apply? The results of ORAL Surveillance do not apply directly to the following subpopulations of patients with rheumatoid arthritis: those younger than 50 years of age, those 50 years of age or older but with no additional cardiovascular risk factors, and those with an incomplete response to or unacceptable side effects from a TNF inhibitor.

Treating rheumatoid arthritis with an effective DMARD is critically important. The use of DMARDs to treat rheumatoid arthritis reduces pain; improves function, quality of life, and productivity; reduces joint destruction and disability; and decreases systemic inflammation. The increase in risk with tofacitinib as compared with TNF inhibitors must be balanced against patient preferences for oral medication.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

From the Medicine Service, Veterans Affairs Medical Center, and the Department of Medicine, School of Medicine, and the

Die drei Säulen des kardiovaskulären Risikomanagements bei Pat. mit chronisch-entzündlichen rheumatologischen Erkrankungen



Journal of Inflammation Research 2021:14 6893–6906

Die drei Säulen des kardiovaskulären Risikomanagements bei Pat. mit chronisch-entzündlichen Autoimmunerkrankungen

1. Effektive Kontrolle des entzündlichen Geschehens
2. Lebensstil-Modifikation insbesondere der beeinflussbaren kardiovaskulären Risikofaktoren
3. Kontrolle der kardiovaskulären Komorbiditäten

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Positive und negative Begleiteffekte der anti-rheumatischen Therapie

NSAIDs (selective/ non selective)	– Blood pressure elevation-Hypertension – CV events (heart failure, acute myocardial infarction, sudden death)
Glucocorticoids	– Impaired metabolic profile (hyperglycemia, insulin resistance)-Prediabetes-Diabetes – Body fat redistribution-obesity – Accelerated atherosclerosis – Blood pressure elevation-Hypertension – Increased incidence of CV events
Methotrexate	– Improvement of metabolic syndrome components – Anti-atherogenic effects – Improved CV outcomes (major CV events, CV mortality) – Hyperhomocysteinemia

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Positive und negative Begleiteffekte der anti-rheumatischen Therapie

Hydroxychloroquine	– Beneficial effects on metabolic profile and related comorbidities (diabetes, dyslipidaemia) – Decreased rates of CV events
Cyclosporine	– Blood pressure elevation-Hypertension – Increased risk of CV and cerebrovascular events
Leflunomide	– Blood pressure elevation-Hypertension
Biologic DMARDs	– Significant reductions in the risk of CV events (myocardial infarction, stroke, and major adverse cardiac events) – Possible deterioration of hypertension – Increased lipid levels
JAK inhibitors	– CV and thromboembolic events – Increased lipid levels

Journal of Inflammation Research 2021:14 6893–6906

Kantonsspital St.Gallen

Rheuma und Herz 2022

Agenda

- **Assoziation zwischen chron. entzündlichen und kardialen Erkrankungen**
- **NSAR und Herz – COX1, COX2 oder was?**
- **Fallbeispiele**
  - Herzinsuffizienz, KHK, Niereninsuffizienz, Vorhofflimmern
- **Fazit**

European Heart Journal (2016) **37**, 1015–1023
doi:10.1093/eurheartj/ehv505

CURRENT OPINION

Cardiovascular safety of non-aspirin non-steroidal anti-inflammatory drugs: review and position paper by the working group for Cardiovascular Pharmacotherapy of the European Society of Cardiology

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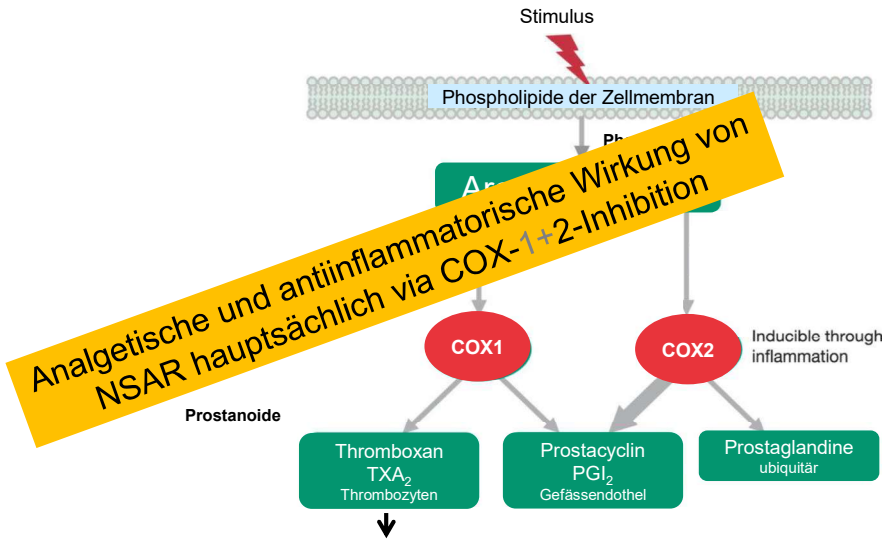
COX 1/2 - Wirkmechanismus



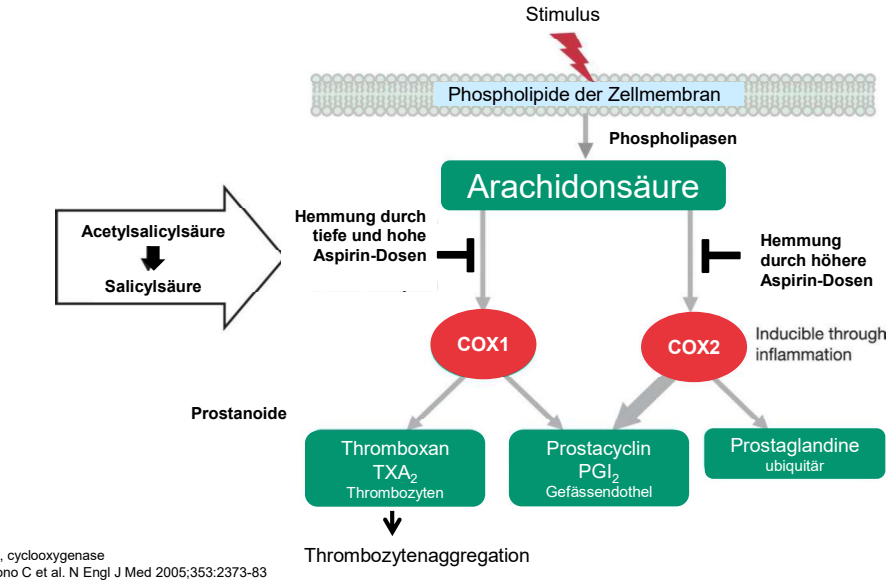
COX, cyclooxygenase
Patrono C et al. N Engl J Med 2005;353:2373-83

Funktion der Cyclooxygenase (COX)

- COX liegt in 2 Formen vor:
  - COX-1 ist in den Blutplättchen vorherrschend und verantwortlich für die Bildung von TXA_2
  - COX-2 ist involviert in die (ubiquitäre) zelluläre Bildung der Prostacycline und Prostaglandine, wie PGI_2 – antipyretisch –antiinflammatorisch - analgetisch
- TXA_2 = wirksamer Aktivator der Thrombozytenaggregation und Vasokonstriktion
  - Interaktion zwischen Blutplättchen und Endothelzellen an den Wänden der Blutgefässe
  - wird durch entgegengesetzte Wirkung von TXA_2 und PGI_2 reguliert, die von der Cyclooxygenase gebildet werden
- PGI_2 = hemmt Thrombozytenaggregation und hat vasodilatorische Wirkung
- Die Aktivierung der Blutplättchen führt zu Anstieg von TXA_2 (vermittelt via COX-1 Enzym) und der Prostaglandine (vermittelt via COX-2 Enzym)

COX, cyclooxygenase; **TXA_2**, thromboxane A_2; **PGI_2**, prostaglandin I_2
Schrör K. Acetylsalicylic acid. Wiley-Blackwell, Germany, 2009; Print ISBN: 9783527321094; Online ISBN: 9783527625994

Wirkmechanismus von Aspirin auf COX 1 und COX1



COX, cyclooxygenase
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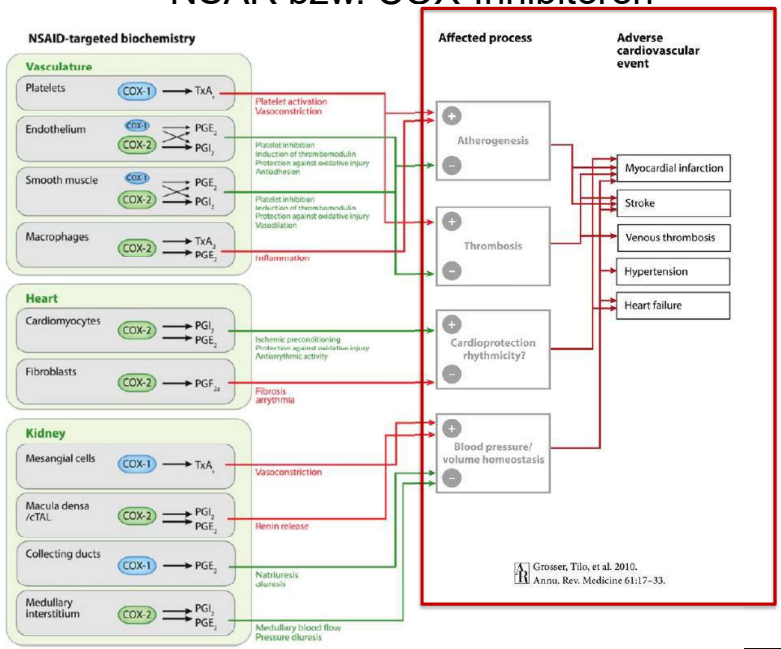
Übersicht ***kardiovaskuläre Nebenwirkungen*** von NSAR bzw. COX-Inhibitoren



Gastro-intestinale NW

- Inhibition der endogenen **COX-1**-vermittelten Prostaglandin-Synthese in den **Mukosa-Zellen des Magens**
  - erhöht Risiko von **gastrointestinaler Toxizität (Dyspepsie, Ulcera, Blutung und Perforation)**
- Limitiert damit den chronischen NSAR-Gebrauch.

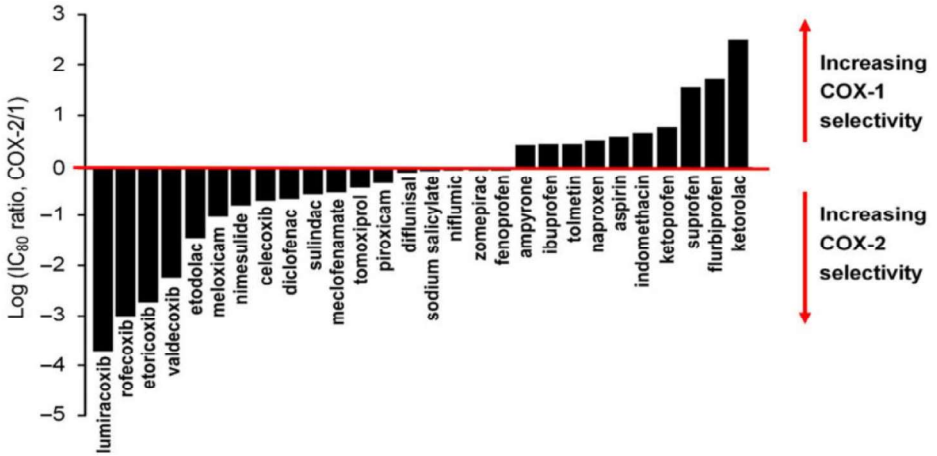
Hoffnung auf COX-2-selektiven NSAR «COX-2-Hypothese»

- «….. Antipyretische, anti-inflammatorische und analgetische Wirkung ohne erhöhtes Risiko von Komplikationen…»
- Coxibe im klinischen Einsatz seit 1998

Kardiovaskuläre Toxizität von COX-2-Inhibitoren

- Akzeleration der Atherogenese
- Blutdruck-Erhöhung
- Risiko von kardialer Dekompensation bei chronischer Herzinsuffizienz
- COX-2-abhängiges Prostacyclin: Proarrhyhtmie

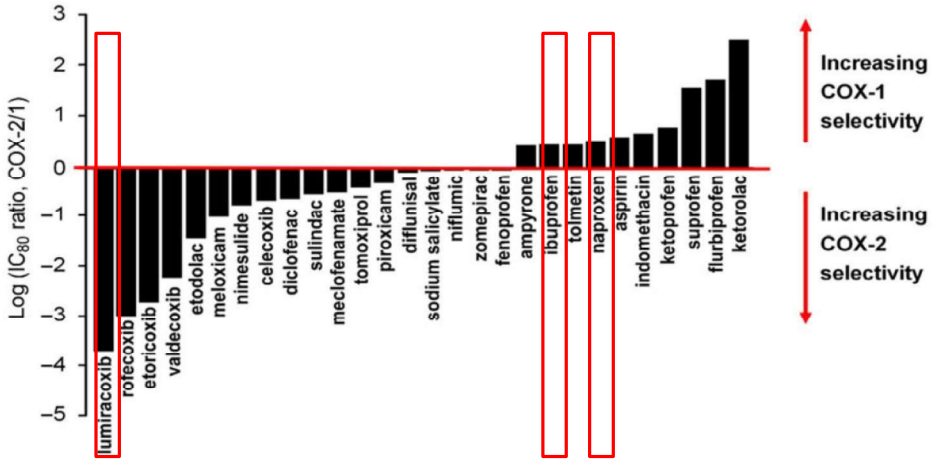
Relative COX-Selektivität von NSAR abhängig von der Konzentration (IC80) welche notwendig ist, die COX-1 und COX-2 Aktivität um 80% zu hemmen



- Es gibt keine absolute COX-Selektivität
- Aspirin: typische Eigenschaft eines nicht selektiven NSAR

European Heart Journal (2016) 37, 1015–1023

Ergebnisse von prospektiv randomisierten Studien am Bsp. lumiracoxib vs. Ibuprofen und Naproxen



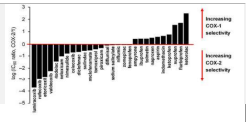
European Heart Journal (2016) 37, 1015–1023

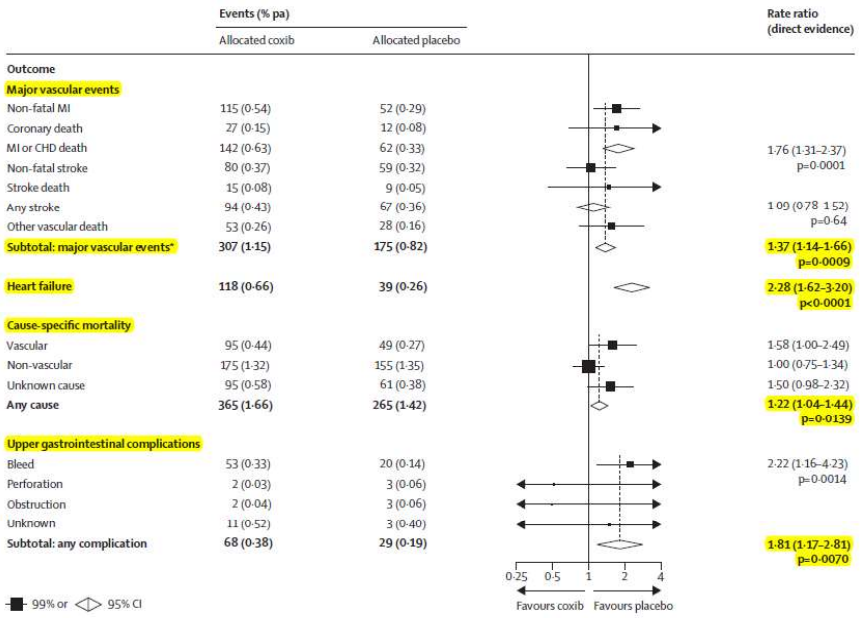
Ergebnisse von prospektiv randomisierten Studien am Bsp. lumiracoxib vs. Ibuprofen und Naproxen

Author, acronym, journal, year	Design, setting, period, and population	Exposures and outcomes (primary/secondary)	Results (95% CI) and limitations
Farkouh *et al.*[37] The TARGET study *Ann Rheum Dis* 2007	RCT (double-blinded, active controls) 29 countries (849 centres) 2001–2002 OA patients ($n = 18\,325$)	Lumiracoxib (400 mg/d) vs. ibuprofen (800 mg t.i.d.) (sub-study 1) or naproxen (500 mg b.i.d.) (sub-study 2) MACE (MI, stroke, CV death)/HF	In high-risk patients using aspirin (75–100 mg/d), MACE risk was higher for ibuprofen (2.14%) vs. lumiracoxib (0.25%) ($P = 0.038$), but similar for naproxen (1.50%) and lumiracoxib (1.40%). In high-risk patients not using aspirin, MACE risk was lower for naproxen (0%) than lumiracoxib (1.57%) ($P = 0.027$), but not ibuprofen vs. lumiracoxib (0.92 vs. 0.80%). Heart failure risk was higher for ibuprofen than lumiracoxib (1.28 vs. 0.14%; $P = 0.031$), but similar for naproxen and lumiracoxib.

Meta-Analyse: Coxibe vs. Placebo

***Lancet* 2013; 382: 769–79**





Evidenz von Beobachtungsstudien

- Erhöhtes kardiovaskuläres Risiko von NSAR unabhängig vom Ausgangs-kardiovaskulären Risiko des untersuchten Kollektivs
- Was heisst das für bestimmte Subgruppen:
  - St.n.Myokardinfarkt ?
  - Herzinsuffizienz?
  - Patienten vor Herzchirurgie und vor nichtkardialen Operationen?
  - Etablierte Thrombocyten-Aggregation?
  - Patienten mit Vorhofflimmern?

Agenda

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  - Herzinsuffizienz, KHK, Vorhofflimmern
- **Fazit**

Herzinfarkt, Herzinsuffizienz

- Alle NSAR verdoppeln Herzinfarkt-Risiko
- Bekannte Herzinsuffienz:
  - Erhöhtes Risiko für Progression, kardiale Dekompensation
  - Dosisabhängig erhöhte Mortalität
  - Pathophysio:
    - Erhöhtes Thromboembolie-Risiko
    - Via renale Effekte
  - Risiko am höchsten bei Coxiben/Diclofenac
  - Risiko unterdurchschnittlich bei Naproxen

Herzinfarkt, Herzinsuffizienz

- Es gibt kein absolut sicheres «NSAR-Fenster» ohne Risikoerhöhung

Nussmeier et al. N Engl J Med 2005;352:1081–1091.
Schjerning Olsen AM, et al. Circulation 2011;123:226–2235.
McGettigan P, et al JAMA 2006;296:1633–1644

Was man vermeiden sollte…

Recommendations	Class[a]	Level[b]	Ref[c]
Thiazolidinediones (glitazones) should not be used as they cause worsening HF and increase the risk of HF hospitalization.	III	A	131–133
Most CCBs (with the exception of amlodipine and felodipine) should not be used as they have a negative inotropic effect and can cause worsening HF.	III	B	134
NSAIDs and COX-2 inhibitors should be avoided if possible as	III	B	135, 136

Recommendation for treatment of patients with HF and arthritis

NSAIDs or COX-2 inhibitors are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization. — III — B

Herzinsuffizie

The addition of an ARB (or renin inhibitor) to the combination of an ACE inhibitor AND a mineralocorticoid antagonist is NOT recommended because of the risk of renal dysfunction and hyperkalaemia.	III	C	–

NSAR und nicht-kardiale Operationen

- NSAR-Gebrauch während/kardialen und nach nicht-kardialen Eingriffen zur Schmerztherapie
  - Naproxen nach Herzchirurgischen Eingriffen ohne wesentlich erhöhtes kardiovaskuläres Risiko

NSAR und nicht-kardiale Operationen

- Etwas kontroverse Ergebnisse
  - Parecoxib und Valdecoxib ohne erhöhtes Thromboembolie-Risiko (1) (aber: sehr wenige Ereignisse)
  - 2.3-fach erhöhtes Risiko (kardiovask. Ereignisse) in Gruppe mit COX-2-Inhibitoren (2)

Guidelines Non-Cardiac surgery: W.mgl. Keine NSAR postoperativ bei KHK und Stroke-Patienten

1) Schug SA, Anesth Analg 2009;108:299–307.
2) Aldington S, N Z Med J 2005;118:U1755.

Antikoagulation und Alter: Das Wichtigste in Kürze

- **Ü 75-Patienten mit Vorhofflimmern Score ≥ 2: Ind für OAK eigentlich immer gegeben**
- **Blutungsrisiko steigt zwar auch mit zunehmendem Alter, aber der absolute Behandlungseffekt bleibt unter DOAK-Therapie erhalten**
- **Wichtig: Modifizierbare RF für Blutung angehen wie**
  - Behandlung der Arteriellen Hypertonie, Vermeidung ergänzender Tc-Aggregationshemmung, NSAR

Chan NC: How I manage anticoagulant therapy in older individuals with atrial fibrillation or venous thromboembolism. Blood 2019; 133: 2269–2278.

NSAR und Gerinnungshemmende Medikamente

- Wenig systematische Daten zu Kombination von NSAR und antithrombotisch wirksamen Medikamenten
- Bei Vo-Fli-Patienten mit OAK-Bedarf, NSAR assoziiert mit erhöhtem Blutungsrisiko
  - 2-3-fach erhöht

- Protonenpumpeninhibitor: 40 mg Pantoprazol po immer während Triple Therapie, bei dualer Therapie bei Risikofaktoren für GI-Blutung (St. n. GI-Blutung, St. n.Ulcus, > 65 J., zusätzliche Einnahme von Steroiden)

Lamberts M et al. Ann Intern Med 2014;161:690–698.

NSAR und Vorhofflimmern

- Rofecoxib assoziiert mit erhöhtem Vorhofflimmer-Risiko (RR 2.90, 95% CI: 1.07–7.88) (1)
- 1.2 bis 1.5-fach erhöhtes Vo-Fli-Risiko
  - Diclofenac mit höherem Risiko als nicht-selektive
  - Herzinsuffizienz-(RR 1.82,95%-CI:1.42-2.32) und Niereninsuff.-Patienten (RR 1.58,95%-CI:1.34-1.85) mit übermässig hohem Risiko (2)

(1) Zhang J et al. JAMA 2006;296:1619–1632
(2) Liu G, Am J Cardiol 2014;114:1523–1529

Public health impact

- Hoher NSAR-Konsum assoziiert mit Myokardinfarkt
- Trotz Guidelines relativ viele Patienten nach Herzinfarkt bzw. bei Herzinsuffizienz NSAR

Agenda

- **Assoziation zwischen chron. entzündlichen und kardialen Erkrankungen**
- **NSAR und Herz – COX1, COX2 oder was?**
- **Fallbeispiele**
  - Herzinsuffizienz, KHK, Vorhofflimmern
- **Fazit**

Gleichgewicht zwischen Benefit und Risiko

- Höhere COX-1-Selektiviät assoziiert mit erhöhtem gastrointestinalem Risiko, aber
- COX-2 Inhibitoren erhöhen Risiko von kardiovskulären Ereignissen
  - 1.8-fach für Coxibe, 1.9-fach für Diclofenac, 4.0-fach für Ibuprofen, and
  - 4.2-fach für Naproxen

Schrittweise Behandlung von muskuloskelettalen Schmerzen mit hohem Kardiovaskulären Risiko