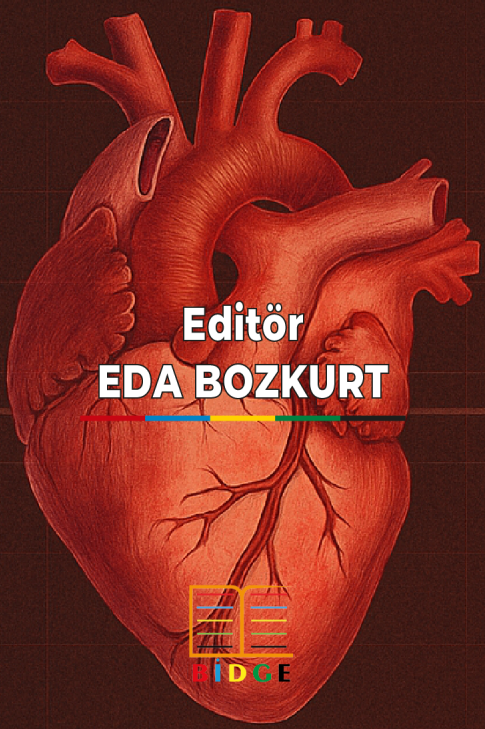
KARDİYOLOJİDE YENİ YAKLAŞIMLAR

SPOR, MİKROBİYOTA, BİYOBELİRTEÇLER ve LDL DIŞI RİSKLERLE DEĞİŞEN KLİNİK PRATİK



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Önsöz

Kardiyolojide Yeni Yaklaşımlar: Spor, Mikrobiyota, Biyobelirteçler ve LDL Dışı Risklerle Değişen Klinik Pratik

Kardiyovasküler hastalıklar, uzun yıllar boyunca klasik risk faktörleri ekseninde ele alındı: hipertansiyon, sigara, LDL kolesterol ve diyabet gibi… Ancak günümüzde bu yaklaşımın ötesine geçen, daha dinamik ve bütüncül bakış açılarına ihtiyaç duyulduğu açıktır. Klinik pratikte karşılaştığımız hasta profili, sadece damar düzeyinde değil; metabolik, inflamatuvar, mikrobiyal ve moleküler düzeyde de değerlendirme gerektirmektedir.

Bu kitap, kardiyolojinin gelişen bu yüzüne ışık tutmayı amaçlamaktadır. Spor kardiyolojisiyle fizyolojik adaptasyon ve aritmi riski arasındaki denge, kalp sağlığının sadece efor kapasitesiyle değil; elektrofizyolojik ve yapısal değişimlerle de izlenmesi gerektiğini göstermektedir. Öte yandan, klasik lipid yaklaşımının ötesine geçerek trigliserid-rich remnant parçacıklar ve Lp(a) gibi parametrelerin rolü, metabolik riskin daha incelikli değerlendirilmesini zorunlu kılmaktadır. Bağırsak mikrobiyotası ise artık sadece bir sindirim sistemi konusu olmaktan çıkmış, endotelyal fonksiyondan inflamasyona kadar geniş bir yelpazede kalp sağlığını etkileyen bir sistem olarak öne çıkmıştır.
Ve son olarak, kalp yetersizliği gibi kompleks sendromlarda biyobelirteçlerin tanı, risk sınıflaması ve tedavi izlemi açısından taşıdığı stratejik değer, modern kardiyolojinin yönünü belirlemektedir. Bu kitapta yer alan bölümler, alanında yetkin akademisyenlerin katkılarıyla hazırlanmış; her biri kanıta dayalı bilgiler, rehber önerileri ve güncel literatürle desteklenmiştir. Amacımız, okuyucuya yalnızca teorik bilgi sunmak değil; aynı zamanda klinik karar süreçlerinde farklı düşünme yolları açmaktır. İnanıyoruz ki bu eser, hem eğitim sürecindeki genç hekimler hem de klinik pratiğini sürekli güncellemek isteyen deneyimli uzmanlar için değerli bir başvuru kaynağı olacaktır. Yeni yaklaşımların ışığında, daha derinlikli bir kardiyoloji pratiğine katkı sunmak dileğiyle…

Editör
Mehmet Serkan ÇETİN
2025

İÇİNDEKİLER

BÖLÜM 1

SPOR KARDİYOLOJİSİ: FİZYOLOJİK ADAPTASYONDAN KLİNİK KARAR SÜREÇLERİNE

1. MEHMET SERKAN ÇETİN[1]

I. GİRİŞ

Spor Kardiyolojisine Genel Bakış

Spor, kardiyovasküler sağlık üzerinde olumlu etkiler yaratmasına rağmen, bazı bireylerde potansiyel kardiyak riskler de barındırabilir. Son yıllarda, düzenli egzersizin kalp sağlığı üzerindeki faydaları yaygın olarak vurgulanırken, yoğun ve profesyonel düzeyde yapılan fiziksel aktivitenin bazı bireylerde ani kardiyak olaylara yol açabileceği anlaşılmıştır. Bu durum, "spor kardiyolojisi" adı altında, hem sağlıklı sporcuların izleminde hem de kardiyak hastalığı olan bireylerin egzersiz yönetiminde uzmanlaşmış bir disiplinin doğmasına yol açmıştır.[1]

Spor Kardiyolojisinin Tanımı ve Gelişimi

[1] Doçent Doktor, Ankara Bilkent Şehir Hastanesi, Kardiyoloji, Orcid: 0000-0002-3983-0496

Spor kardiyolojisi, rekabetçi ya da rekabet dışı olarak fiziksel aktivite yapan bireylerde kardiyovasküler sağlığı korumayı, ani kardiyak ölüm gibi nadir fakat ciddi sonuçları önlemeyi ve aynı zamanda hastalığı olan bireylerde güvenli egzersiz reçeteleri sunmayı amaçlayan multidisipliner bir alt uzmanlık alanıdır.[2] İlk olarak 1980'lerde, ani kardiyak ölümlerin televizyon ekranlarında canlı yayınlanan spor müsabakalarında görülmeye başlamasıyla dikkat çekmiş, 2000'li yıllarda ise rehberlere girerek kurumsallaşmıştır.

Artan Klinik İhtiyaç

Spor yapan bireylerde kalp hastalıklarının önceden saptanması, sadece bireysel değil toplumsal sağlık açısından da önemlidir. Günümüzde rekabetçi sporcuların yanı sıra, orta yaş üstü bireyler de maraton, triatlon gibi ekstrem aktivitelere yönelmektedir. Bu grup; hipertansiyon, diyabet ve gizli koroner arter hastalığı gibi risk faktörleriyle spor kardiyolojisi pratiğinde önemli bir yer tutmaktadır.[3]

Ek olarak, kardiyak hastalığı olup da spor yapmak isteyen bireylerde de uygun aktivite düzeyinin belirlenmesi, komplikasyonların önlenmesi açısından zorunlu hâle gelmiştir. Kalp yetersizliği, aritmi ya da kardiyomiyopati tanısı alan bireylerde egzersiz kapasitesinin doğru değerlendirilmesi ve tedaviye entegrasyonu hem yaşam kalitesini hem de prognozu etkilemektedir.[4]

Gelişen Tanı ve İzlem Yöntemleri

Günümüzde spor kardiyolojisi uygulamaları, sadece klasik EKG ve efor testleriyle sınırlı değildir. Ekokardiyografi, kardiyak MR, ileri düzey ritim izlem sistemleri, genetik testler ve giyilebilir teknolojiler bu alanda yaygın olarak kullanılmaktadır.[5] Ayrıca, Avrupa Kardiyoloji Derneği (ESC) ve Amerikan Kalp Derneği (AHA) rehberlerinde sporcular için özel tanısal algoritmalar

oluşturulmuş ve hangi bulgunun ne zaman patolojik olduğu daha açık şekilde tanımlanmıştır.[6-7]

Spor Kardiyolojisinin Hedef Kitlesi

- Profesyonel sporcular
- Genç rekabetçi sporcular
- Yüksek riskli orta yaşlı sporcular
- Kardiyak hastalığı olan ve spor yapmak isteyen bireyler
- Kardiyovasküler rehabilitasyon sürecinde olan hastalar
- Egzersize bağlı semptomu olan sedanter bireyler

Multidisipliner Yaklaşımın Önemi

Spor kardiyolojisi pratiği, yalnızca kardiyologlar değil; spor hekimleri, fizyoterapistler, egzersiz fizyologları, antrenörler ve beslenme uzmanları ile entegre çalışmayı gerektirir. Bu ekip çalışması sayesinde bireyin sağlık durumu bütüncül olarak değerlendirilir ve en uygun fiziksel aktivite modeli belirlenebilir.

II. EGZERSİZİN KARDİYOVASKÜLER SİSTEM ÜZERİNDEKİ ETKİLERİ

Egzersiz, kardiyovasküler sistem üzerinde hem akut hem de kronik düzeyde çok sayıda fizyolojik adaptasyonu tetikler. Bu adaptasyonlar, egzersizin süresine, yoğunluğuna, türüne ve sıklığına bağlı olarak değişiklik gösterir. Düzenli fiziksel aktivite kardiyovasküler mortaliteyi azaltırken, performans düzeyine ulaşmak adına yapılan aşırı efor, belirli bireylerde patolojik süreçleri de tetikleyebilir.[8]

Kardiyak Adaptasyonlar

a. Sol Ventrikül Adaptasyonları

Dayanıklılık sporcularında sol ventrikül hem kavite çapı hem de duvar kalınlığı açısından büyür. Bu fizyolojik hipertrofi, genellikle eksantrik hipertrofi (hacim yükü) şeklindedir. Buna karşın kuvvet sporlarında (halter, güreş), konsantrik hipertrofi (basınç yükü) daha ön plandadır.[9] Atlet kalbinde sol ventrikül diyastolik çapı >55 mm'ye kadar çıkabilirken, ejeksiyon fraksiyonu genellikle normal veya yüksek-normal düzeyde kalır.

b. Sağ Ventrikül Adaptasyonları

Sağ ventrikül (RV) hacmi, dayanıklılık sporlarında anlamlı şekilde artar. Ancak bu fizyolojik genişleme ile aritmogenik sağ ventrikül kardiyomiyopatisi (ARVC) arasında ayrım yapmak klinik açıdan kritiktir. Egzersize bağlı sağ ventrikül strain bozulması bazı çalışmalarda aritmi riskiyle ilişkilendirilmiştir.[10]

Şekil 1. Egzersizin Kalpte Etkileri

Hemodinamik Değişiklikler

Egzersiz sırasında:

- Kalp hızı (HR) ve atım hacmi (SV) artar → kalp debisi (CO) yükselir
- Periferik vasküler direnç azalır
- Sistolik kan basıncı artar, diyastolik basınç sabit kalabilir veya hafif düşer

Bu yanıtlar sayesinde kaslara oksijen taşınımı artırılır. Eğitimli bireylerde istirahat kalp hızı azalır ve nabız basıncı genişler. Maksimal egzersiz sırasında kardiyak debi 20–40 L/dk'ya kadar ulaşabilir.[11]

Vasküler Adaptasyonlar

Uzun dönem egzersiz, endotel fonksiyonunu artırarak arteriyel elastisiteyi geliştirir. Flow-mediated dilatation (FMD) gibi parametrelerde artış gözlenir. Ayrıca, egzersizle birlikte antiinflamatuvar sitokin düzeylerinde yükselme, CRP ve IL-6 gibi inflamatuvar belirteçlerde azalma görülür.[12]

Otonom Sinir Sistemi Üzerindeki Etkiler

Düzenli egzersiz parasempatik tonusu artırır, sempatik aktiviteyi baskılar. Bu değişiklikler:

- Kalp hızında azalma
- Kalp hızı değişkenliğinde (HRV) artış
- Barorefleks duyarlılığında iyileşme

gibi yararlar sağlar. Bu etkiler, kardiyak aritmilere karşı koruyucudur.[13]

Tablo 1. Egzersiz Tipine Göre Etkiler

Egzersiz Türü	**Ana Kardiyak Etki**	**Ventrikül Adaptasyonu**
Dayanıklılık	Hacim yükü → eksantrik hipertrofi	Sol ve sağ ventrikülde dilatasyon
Kuvvet (Resistance)	Basınç yükü → konsantrik hipertrofi	Duvar kalınlığında artış
Karma (futbol, basketbol)	Hem hacim hem basınç yükü kombinasyonu	Dengesiz ventrikül yanıtı olası

Kronik Adaptasyonun Sınırları: "Atlet Kalbi" mi, "Gizli Hastalık" mı?

Yoğun egzersiz yapan bireylerde görülen kardiyak adaptasyonların çoğu fizyolojik olsa da, bazı olgularda maskelenmiş kardiyomiyopati, subklinik miyokardit, veya genetik aritmi sendromları ayırt edilemeyebilir. Özellikle asimetrik hipertrofi, ejeksiyon fraksiyonunda düşüş, aritmi varlığı, veya anormal strain bulguları varsa ileri tetkikler gerekir.

Sonuç olarak egzersiz, kalp ve damar sisteminde geniş çaplı uyum mekanizmalarını tetikler. Bu adaptasyonlar bireyin egzersiz tipine ve süresine göre değişiklik gösterir. Ancak kardiyolojik

izlemin bu süreçleri ayırt edebilecek bilgi ve donanıma sahip olması gerekir. Özellikle spora dönüş kararlarında bu fizyolojik adaptasyonlarla patolojik değişikliklerin ayrımı yaşamsal önem taşır.

III. SPORCULARDA KARDİYAK ANATOMİK VE ELEKTROFİZYOLOJİK ADAPTASYONLAR

Düzenli egzersiz yapan bireylerde kalp, kardiyak iş yüküne karşı adaptif bir yanıt verir. Bu adaptasyonlar anatomik düzeyde kalp hacmi ve duvar kalınlığında değişimlere neden olurken, elektrofizyolojik düzeyde EKG bulgularında belirgin farklılıklarla kendini gösterebilir. Bu değişikliklerin fizyolojik mi yoksa patolojik mi olduğu, sporcu izleminin en kritik sorularından biridir.[1]

Anatomik Adaptasyonlar

a. Sol Ventrikül

Dayanıklılık sporcularında sol ventrikül kavite çapı genişler ve duvar kalınlığı artar. Genellikle duvar kalınlığı 12–16 mm arasında olup simetrik hipertrofi şeklindedir. Bu durum, hipertrofik kardiyomiyopatiden ayırt edilmelidir.

Tablo 2. Atlet Kalbi ve Hipertrofik Kardiyomiyopatinin Ayrılması

Özellik	**Atlet Kalbi**	**Hipertrofik Kardiyomiyopati**
Duvar Kalınlığı	≤16 mm	Genellikle ≥15 mm

Sol Ventrikül Kavitesi	Genişlemiş	Normal/küçük
Diastolik Fonksiyon	Normal/supernormal	Bozulmuş
Aile Öyküsü / Genetik	Negatif	Sıklıkla pozitif
Değişkenlik	Egzersiz kesilince gerileyebilir	Kalıcı

b. Sağ Ventrikül

Sağ ventrikül dilatasyonu, dayanıklılık sporcularında belirgindir ve genellikle sol ventrikülde gözlenen adaptasyonlarla paralel seyreder. Ancak ARVC gibi hastalıklarla ayrım klinik olarak zordur. Özellikle RV bazal çapının >42 mm, düşük strain ve ventriküler aritmi varlığı patoloji düşündürmelidir.[10]

Elektrofizyolojik Adaptasyonlar

Egzersizle birlikte kalpte otonomik denge parasempatik yönü artacak şekilde değişir. Bu durum sinüs bradikardisi, atriyoventriküler ileti gecikmesi ve bazı ektopik atımların normal sayılmasını sağlar.

a. Normal Sporcu EKG Bulguları[14-15]

- Sinüs bradikardisi (<50 bpm)
- Birinci derece AV blok (PR 200–300 ms)
- İnkomplet sağ dal bloğu

- İzole voltaj artışları (Sokolow-Lyon)
- Erken repolarizasyon (özellikle inferolateral derivasyonlarda)
- Juvenil T-dalgası inversiyonları (V1–V3)
- Artmış QRS voltajı

b. Patolojik EKG Bulguları (İleri İnceleme Gerektirir)

- T dalgası inversiyonu (özellikle V4 ve ötesinde)
- ST segment depresyonu
- Patolojik Q dalgaları
- QTc >470 ms (erkek) / >480 ms (kadın)
- Mobitz II blok, 2:1 AV blok
- Ventriküler preeksitasyon (WPW)
- Brugada paterni
- Ventriküler taşikardi (VT) atımları

Cinsiyet ve Etnik Farklılıklar

a. Cinsiyete Bağlı Farklılıklar

- Kadın sporcularda sol ventrikül hipertrofisi ve voltaj yüksekliği daha az belirgindir.
- Erkeklerde bradikardi ve EKG voltaj artışı daha sık gözlenir.

b. Etnik Farklılıklar

- Siyahi sporcularda anterolateral derivasyonlarda T-dalgası inversiyonu ve yüksek voltaj daha sık görülür.

- Bu bulguların patolojik mi yoksa varyant mı olduğu, etnik farklılıklar dikkate alınarak değerlendirilmelidir.[16]

Tablo 3. Sporcularda Sıklıkla Görülen EKG Bulguları

Durum	**EKG Özelliği**	**Değerlendirme**
Sinüs bradikardisi	Kalp hızı <50 bpm	Fizyolojik olabilir
İnkomplet RBBB	rsR' patern V1'de	Yaygın ve benign
T inversiyonu V1-V2	Genç bireyde, simetrik, izole	Fizyolojik olabilir
T inversiyonu V4-V6	Özellikle inferolateral bölgede	Patolojik düşünülmeli

Ayırıcı Tanıda Ekokardiyografi ve Kardiyak MR

Sporcularda şüpheli EKG veya fizik muayene bulgusu saptandığında, ekokardiyografi ilk basamak testtir. Ancak:

- Duvar kalınlığının 13–16 mm olduğu "gri bölge" olgularında,
- Segmental duvar hareket bozukluğu varsa,
- Strain analizi bozulmuşsa,

kardiyak MR tanısal değeri artırır. Late gadolinium enhancement (LGE) varlığı, fibrozis göstergesi olup patolojiyi destekler.[17]

Sonuç olarak sporcularda gözlenen kardiyak anatomik ve elektrofizyolojik adaptasyonlar fizyolojik değişimlerin sonucu olabilir. Ancak, bazı bulgular altında yatan ciddi kardiyak hastalıkların ilk belirtisi olabilir. Bu nedenle, fizyolojik varyantlarla patolojik bulguların ayrımı spor kardiyolojisinin temel taşlarından biridir.

IV. ANİ KARDİYAK ÖLÜM VE SPOR

Ani kardiyak ölüm (AKÖ), sporcularda nadir görülen ancak son derece dramatik ve travmatik bir olaydır. Medyada sıkça yer alan bu olaylar, spor kardiyolojisinin doğuşuna ve gelişimine doğrudan katkıda bulunmuştur. Sporcuda meydana gelen ani ölüm olgularının çoğu, altta yatan sessiz bir kardiyovasküler hastalığın ilk ve tek belirtisidir.[18]

Tanım ve Epidemiyoloji

Ani kardiyak ölüm, genellikle semptomsuz bir bireyde, başlangıç semptomundan sonraki bir saat içinde kardiyak nedenli ve beklenmedik şekilde gerçekleşen ölüm olarak tanımlanır.[19] Spor sırasında veya hemen sonrasında görülmesi durumunda egzersize bağlı AKÖ'den söz edilir.

- Genel popülasyonda AKÖ insidansı ≈ 1–2/100.000 kişi-yıl
- Rekabetçi sporcularda ≈ 0.5–1/100.000 sporcu-yıl
- Erkeklerde, özellikle siyahi ve genç sporcularda risk daha yüksektir

- Spora bağlı ani ölümün %75'i egzersiz sırasında, %25'i dinlenme döneminde meydana gelir

Etiyolojik Nedenler

Ani ölüm nedenleri yaşa göre değişir:

a. Genç Sporcularda (<35 yaş) En Sık Nedenler (Tablo 4):

Tablo 4. Genç Sporcularda Ani Kardiyak Ölüm Nedenleri

Hastalık	**Açıklama**
Hipertrofik Kardiyomiyopati (HCM)	Genetik, miyofibril protein bozukluğu; özellikle septal hipertrofi ile karakterizedir.
Aritmojenik Sağ Ventrikül Kardiyomiyopatisi (ARVC)	Sağ ventrikülde fibrofat infiltrasyon; V1-V3'de T inversiyonları ve VT atakları ile seyreder.
Koroner Arter Anomalileri	Özellikle sol koronerin aort ile pulmoner arter arasından geçmesi risklidir.
Kongenital LQTS, CPVT, Brugada Sendromu	İyon kanal hastalıkları; sıklıkla polimorfik VT ve senkop ile başlar.

Miyokardit	Viral nedenli subklinik inflamasyon; egzersizle tetiklenmiş aritmiye yol açabilir.

b. Yaşlı Sporcularda (>35 yaş):

- En sık neden: Koroner Arter Hastalığı (KAH)
- Özellikle kontrolsüz risk faktörleri olan bireylerde egzersizle tetiklenen MI ve aritmi
- AKÖ'nin bu yaş grubundaki %70'inden fazlası KAH'ye bağlıdır[20]

Sporla İlişkili Tetikleyici Mekanizmalar

- Artan sempatik tonus
- Elektrolit dengesizlikleri (özellikle hipokalemi)
- Dehidratasyon
- Subklinik fibrozis veya inflamasyonun aritmi oluşturması
- KAH varlığında plak rüptürü ve tromboz

Egzersiz, predispozan hastalığı olan bireyde ölümcül aritmiye neden olabilir.

Tarama ve Önleme Stratejileri

a. Spora Katılım Öncesi Tarama (Pre-participation Screening)

Amaç: Sessiz kardiyak hastalıkları tespit ederek ani ölüm riskini azaltmak

Tablo 5. Spora Katılım Öncesi Değerlendirme Yöntemleri

Yöntem	**Etkililik**	**Öneri Kaynağı**
Anamnez + Fizik Muayene	Orta düzeyde duyarlılık	AHA önerisi
12 Derivasyonlu EKG	%70–90 duyarlılık	ESC önerisi
Ekokardiyografi (seçilmiş)	HCM, ARVC ayırıcı tanısı	Klinik endikasyonla

- **ESC** (2020): EKG taramasını önerir [6]
- **AHA/ACC** (2015): Standart anket ve fizik muayene önerir, EKG'yi opsiyonel bırakır [7]

b. Seattle ve International EKG Kriterleri

EKG varyasyonlarının daha iyi sınıflandırılması amacıyla 2013 Seattle Kriterleri, 2017 International Consensus Kriterleri geliştirilmiştir. Bu kriterler ile "normal varyant" ve "patolojik bulgu" ayrımı daha güvenilir hale gelmiştir.[1]

Otomatik Eksternal Defibrilatör (OED) ve Acil Müdahale

Ani kardiyak ölüm riskinin tamamen ortadan kaldırılması mümkün olmasa da, spor alanlarında OED cihazlarının bulunması ve acil eylem planlarının olması mortaliteyi ciddi ölçüde azaltır.

- Defibrilasyonun ilk 3 dakika içinde yapılması, sağkalımı %70'e çıkarabilir.
- Bu nedenle, spor salonları, okullar ve stadyumlarda OED kullanımı teşvik edilmelidir.[21]

Hukuki ve Etik Boyutlar

Sporcunun kariyerini sonlandırabilecek bir kardiyak hastalığın saptanması, sadece tıbbi değil, etik ve psikososyal bir sorumluluk doğurur. Karar verme sürecinde sporcu, ailesi, antrenör ve sağlık profesyonelleri ortak bir değerlendirme yapmalıdır. Bazı ülkelerde tarama zorunlu iken (İtalya), bazılarında bu karar bireye bırakılmıştır.

Sonuç olarak, sporcularda ani kardiyak ölüm, önlenebilir ancak tamamen ortadan kaldırılamaz bir risktir. En sık nedenler yaşa göre değişmekle birlikte, kapsamlı tarama, uygun ekipman ve bilinçli egzersiz uygulamaları bu riski en aza indirebilir. Rehberlerin ötesinde, her sporcu bireysel olarak değerlendirilmelidir.

V. SPORCULARDA KARDİYAK HASTALIKLAR

Sporcularda kardiyak hastalıkların varlığı hem performansı hem de yaşamı tehdit edebilecek potansiyel taşıdığı için titizlikle değerlendirilmelidir. Bu hastalıkların bazıları egzersize bağlı komplikasyonlara yol açarken, bazıları ise yalnızca tarama sırasında fark edilen sinsi seyirli patolojilerdir.

Hipertrofik Kardiyomiyopati (HCM)

HCM, sol ventrikül duvar kalınlığının miyofibril protein mutasyonları sonucu belirgin şekilde artmasıyla karakterizedir. Genetik geçişli, otozomal dominant bir hastalıktır. Egzersizle tetiklenebilecek ventriküler aritmi ve ani ölüm riski nedeniyle sporda en kritik patolojilerden biridir.[22]

Sporcu Kalbinden Ayırıcı Tanı

- Duvar kalınlığı genellikle >15 mm
- Asimetrik hipertrofi (özellikle septal)
- Diyastolik disfonksiyon ve sol atriyum dilatasyonu
- LGE pozitifliği
- Aile öyküsü ve ani ölüm riski
- Spora Katılım
- Yüksek riskli olgularda rekabetçi sporlara katılım önerilmez.
- ICD varlığı, senkop öyküsü, VT varlığı gibi parametreler dışlama nedenidir.

Aritmojenik Sağ Ventrikül Kardiyomiyopatisi (ARVC)

ARVC, sağ ventrikülün fibrofat infiltrasyonu ile karakterizedir. Genç sporcularda ani ölüm nedenidir. Egzersiz bu hastalığın ilerlemesini hızlandırabilir.[23]

Tanı Kriterleri

- V1–V3 T inversiyonu
- Epsilon dalgaları
- Non-sustained VT (NSVT)

- Kardiyak MR ile sağ ventrikül disfonksiyonu
- Genetik mutasyon (plakofilin, desmoplakin)

- Spora Katılım
- ARVC tanısı olan bireylerde tüm rekabetçi sporlardan men önerilir (Class I, ESC 2020).

Koroner Arter Anomalileri

Doğumsal koroner arter anomalileri, özellikle sol koroner arterin sağ sinüs çıkışından gelip aort ile pulmoner arter arasından geçmesi durumunda ani kardiyak ölüm riskini artırır.

Bulgular

- Egzersize bağlı göğüs ağrısı, senkop
- İskemik EKG bulguları
- CT anjiyografi ile tanı

Spora Katılım

- Cerrahi düzeltme sonrası asemptomatik bireylerde, post-op risk değerlendirmesine göre karar verilir.

Dilate Kardiyomiyopati (DCM)

- Sol ventrikül çapı artmış, EF düşüktür
- Aritmi ve emboli riski yüksektir
- Rekabetçi spor önerilmez (EF <50% ise özellikle)

Kanalopatiler

a. Uzun QT Sendromu (LQTS)

- QTc >470 ms (erkek), >480 ms (kadın)
- Egzersizle torsades de pointes tetiklenebilir
- Beta bloker tedavisi, bazı olgularda ICD önerilir
- Yüzme, sıçrama içeren sporlarda risk yüksektir[24]

b. Brugada Sendromu

- Tip 1 Brugada paterni + ventriküler aritmi riski
- Egzersizin ısı artışı ve sempatik tonusu artırmasıyla tetiklenebilir
- Yüksek riskli bireylerde spor önerilmez

c. CPVT (Catecholaminergic Polymorphic VT)

- Egzersize bağlı polimorfik VT, senkop
- Normal yapıda kalp, stresle tetiklenen aritmi
- Mutlak spor kısıtlaması gerekir

d. Miyokardit

- Viral enfeksiyon sonrası subklinik inflamasyon
- Ciddi aritmilere neden olabilir
- MR'da LGE ve ödem bulguları tanısaldır
- Spor yasağı: Tanıdan sonra minimum 3–6 ay egzersizden uzak kalınmalı[25]

Prematür Ventriküler Kompleksler (PVC) ve Non-Sustained VT

- %1'den fazla PVC veya çok morfolojili PVC varlığı patoloji lehine yorumlanır
- Özellikle egzersiz sırasında artan PVC'ler incelemeye değer
- Ekokardiyografi + MR ile yapısal hastalık dışlanmalıdır
- İyi huylu PVC'lerde spora devam mümkündür

Supraventriküler Taşikardiler ve Wolf Parkinson White Sendromu

a. AVNRT, AVRT

- Çoğu iyi huyludur
- Sıklıkla semptomatiktir ancak ani ölüm riski düşüktür
- Ablasyon sonrası spora dönüş genellikle sorunsuzdur

b. WPW Sendromu

- Aksesuar yol varlığı
- R-R kısa, delta dalgası, geniş QRS
- Atriyal fibrilasyon gelişirse ani ölüm riski
- Spor öncesi EPS önerilir, ablasyon sonrası spor serbest olabilir

Atriyal Fibrilasyon (AF)

- Dayanıklılık sporcularında daha sık görülür
- Vagal tonus artışı ve atriyal dilatasyon rol oynar
- Spora dönüş, ablasyon veya medikal kontrol sonrası mümkündür
- Antikoagülasyon kararı bireysel verilmelidir

Kalp Yetersizliği ve Cihazlı Sporcular (ICD, Pacemaker)

- EF <50% olan bireylerde yüksek efor önerilmez
- ICD varlığında spora dönüş kararları rehber eşliğinde verilir
- Cihaz yerleşimi, temas riski ve cihaz ayarları göz önünde bulundurulmalıdır

Doğumsal Kalp Hastalıkları

- Düşük riskli lezyonlar (ASD küçük çaplı) ile spor yapılabilir
- Post-op durumlarda her hasta bireysel değerlendirilmelidir

VI. SPORA DÖNÜŞ KARARLARI

Kardiyovasküler hastalık geçirmiş bireylerde spora dönüş kararı, yalnızca egzersiz kapasitesine değil; aynı zamanda aritmi riski, miyokard iyileşmesi, cihaz varlığı ve bireysel özelliklere göre verilmelidir. Son yıllarda ESC ve AHA tarafından yayımlanan

rehberler, bu konuda daha net algoritmalar sunmaktadır. Ancak her hasta için bireyselleştirilmiş bir yaklaşım esastır.[26]

Tablo 6. Spora Dönüş Değerlendirme Basamakları

Değerlendirme Alanı	**Örnek Araçlar**
Klinik iyileşme	Semptom sorgulama, NYHA sınıfı
Yapısal iyileşme	EKO, MR
Ritim analizi	Holter, egzersiz testi
Egzersiz kapasitesi	Kardiyopulmoner egzersiz testi (CPET)
Aritmi riski	EPS, ICD kayıtları
İlaç uyumu ve yan etki profili	Klinik takip

Temel Hastalıklara Göre Spora Dönüş Kriterleri

a. Hipertrofik Kardiyomiyopati

- Düşük riskli, asemptomatik bireylerde düşük-orta düzeyde rekabet dışı sporlar izinli olabilir.
- İzlem: MR ile fibrozis yokluğu, normal holter, VT yokluğu, senkop yokluğu

- ESC 2020: "Seçili bireylerde paydaşlı karar verilerek bazı sporlar izinli olabilir" (Class IIb) [27]

b. ARVC

- Tüm rekabetçi sporlar kontrendikedir (Class III)
- Günlük fiziksel aktivite kısıtlanmalıdır

c. Miyokardit

- Tanı sonrası minimum 3–6 ay spor yasağı
- Spora dönüş için:
  - EF >50%
  - Troponin normal
  - MR'da rezidüel ödem veya LGE yokluğu
  - Ritim normal (Holter/CPET) [25]

d. Koroner Arter Hastalığı / MI

- Revaskülarizasyon sonrası düşük riskli bireylerde 1–3 ay içinde dönüş planlanabilir
- CPET ile iskemik eşik belirlenmeli
- Stabil anti-iskemik tedavi altında olmalı

e. Aritmiler (SVT, AF, PVC)

- Ablasyon sonrası rekabetçi spora dönüş genellikle 4–6 hafta içinde mümkündür

- Persistan aritmi durumunda antiaritmik tedavi yanıtı gözlenmelidir
- Antikoagülasyon gereken bireylerde temas sporlarından kaçınılmalıdır

f. ICD / Cihazlı Hastalar

- ESC 2020: Seçilmiş hastalarda, cihaz ayarları optimize edilerek düşük temaslı sporlara izin verilebilir
- Temas riski yüksek sporlardan kaçınılmalı (futbol, dövüş sporları)
- Egzersiz sırasında uygun şok riski taşıyan bireyler için spordan men önerilir[27]

Tablo 7. Spora Dönüşte Risk Sınıflaması

Risk Sınıfı	**Özellikler**	**Spor Önerisi**
Düşük risk	Yapısal hastalık yok, semptom yok, EKG normal	Tüm sporlar (bireysel karar)
Orta risk	Hafif yapısal değişiklik, kontrol altındaki aritmi	İzlem altında bireysel planlama
Yüksek risk	LGE pozitif, ciddi aritmi, EF <50%, semptomatik hastalık, ICD varlığı	Rekabetçi sporlardan men

Karar Verme Süreci: Paydaşlı Yaklaşım

Sporcularda veya aktif bireylerde spora dönüş kararı yalnızca klinik temelli değil, psikososyal ve hukuki yönleriyle de ele alınmalıdır. Bu nedenle karar şu paydaşlar arasında paylaşılmalıdır:

- Kardiyolog
- Spor hekimi
- Antrenör / kulüp doktoru
- Hasta ve ailesi
- Gerekirse psikolog

Bu süreçte, özellikle "belirsiz risk taşıyan" bireylerde karar hasta ile birlikte alınmalıdır. ESC 2020 rehberinde bu yaklaşım "shared decision-making" olarak tanımlanmıştır.

Spora Dönüşte CPET ve Holter Rolü

- **CPET (Kardiyopulmoner Egzersiz Testi):** Spesifik VO2 ölçümleri ile fonksiyonel kapasiteyi gösterir. Anaerobik eşik, kardiyak rezerve dair bilgi verir.

- **Holter:** Sessiz aritmi taraması için kritiktir. Egzersiz sırasında artan PVC, VT gibi bulgular varsa ileri tetkik gerekir.

Sonuç olarak spora dönüş süreci, sabit bir algoritma yerine bireysel risk faktörleri, egzersiz tipi ve klinik stabiliteye göre planlanmalıdır. Kardiyak hastalık geçirmiş bireylerde rekabetçi spora dönüş sadece medikal değil, etik ve hukuki bir değerlendirme de içerir. Her karar multidisipliner bir çerçevede, hasta merkezli olarak verilmelidir.

VII. KARDİYOPROTEKTİF EGZERSİZ REÇETESİ VE REHABİLİTASYON

Düzenli egzersiz, kardiyovasküler hastalıkların önlenmesi ve tedavisinde önemli bir bileşendir. Fiziksel aktivite, sadece kardiyak risk faktörlerini azaltmakla kalmaz, aynı zamanda vasküler fonksiyonu iyileştirir, inflamasyonu azaltır ve yaşam kalitesini artırır. Kardiyoprotektif etkinin maksimum düzeyde sağlanabilmesi için egzersizin bilimsel temellere dayalı olarak bireyselleştirilmesi gereklidir.[28]

Egzersiz Reçetelendirme: FITT Prensibi

Egzersiz reçetesi oluşturulurken kullanılan temel yaklaşım **FITT** prensibidir:

Tablo 8. FITT Prensibi

Bileşen	**Açılımı**	**Uygulama Örneği**
Frequency	Haftalık sıklık	Haftada 3–5 gün
Intensity	Egzersiz şiddeti	%50–80 VO_2max, Borg skalası 12–16 arası
Time	Süre	30–60 dakika / seans

Type	Egzersiz türü	Yürüyüş, bisiklet, yüzme, direnç egzersizleri

Not: Başlangıç seviyesinde olan bireylerde süre ve şiddet daha düşük düzeyde başlatılır, zamanla artırılır.

Kardiyovasküler Risk Gruplarına Göre Egzersiz Planlaması

a. Düşük Riskli Bireyler

- Medikal engel yok
- Egzersiz reçetesi minimal izlemle uygulanabilir
- Egzersiz öncesi kardiyolojik tarama önerilir ama zorunlu değildir

b. Orta ve Yüksek Riskli Bireyler

- Geçirilmiş MI, PCI, CABG, EF <50%, aritmi öyküsü
- Egzersiz öncesi:
  - CPET (kardiyopulmoner egzersiz testi)
  - Holter
  - Ekokardiyografi ile değerlendirme önerilir
- Başlangıçta medikal gözetim altında egzersiz (kardiyak rehabilitasyon faz II) [4,29]

Tablo 9. Egzersizin Kardiyoprotektif Etkileri

Etki Alanı	**Etki Mekanizması**

Kan basıncı	Endotel fonksiyonunun iyileşmesi, NO artışı
Kan şekeri kontrolü	İnsülin duyarlılığında artış, glukoz transportu
Lipidler	HDL artışı, trigliserid düşüşü
Otonom denge	Parasempatik tonus artışı, HRV artışı
Ventrikül fonksiyonu	LV strain parametrelerinde iyileşme
Enflamasyon	CRP, IL-6 gibi inflamatuvar markerlerde azalma

Kardiyak Rehabilitasyonun Basamakları

Faz I: Akut dönem (hastanede başlar)

- Yatak içi mobilizasyon
- Vital bulgu kontrolü eşliğinde kısa yürüyüşler
- Bilgilendirme ve hasta eğitimi

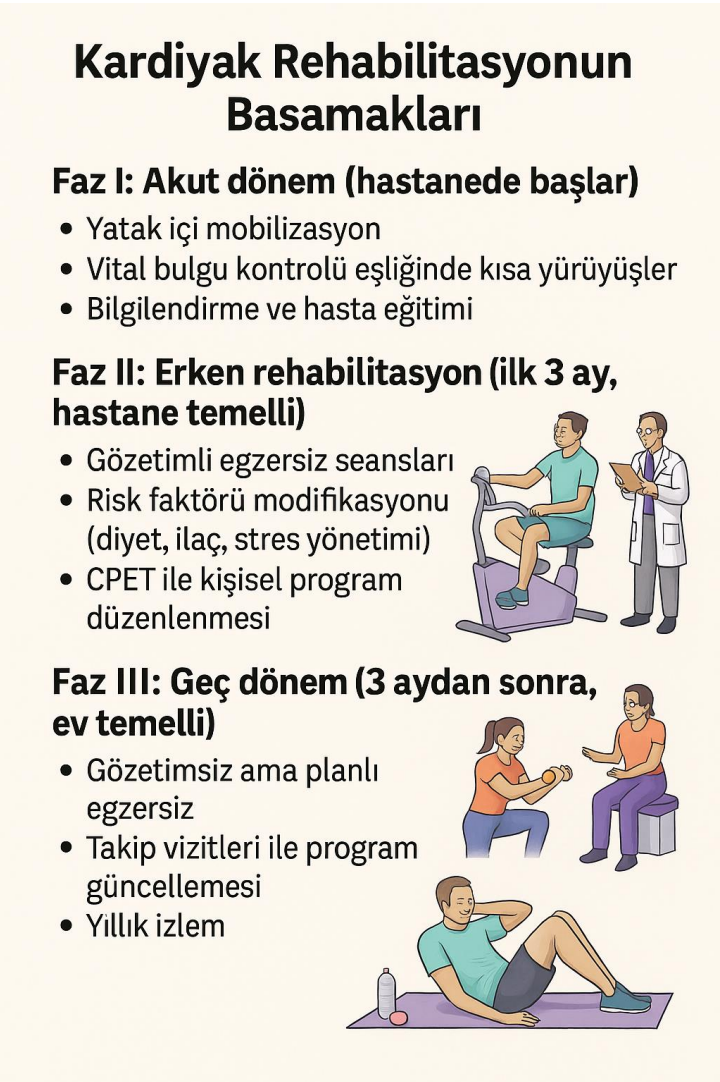
Faz II: Erken rehabilitasyon (ilk 3 ay, hastane temelli)

- Gözetimli egzersiz seansları
- Risk faktörü modifikasyonu (diyet, ilaç, stres yönetimi)
- CPET ile kişisel program düzenlenmesi

Faz III: Geç dönem (3 aydan sonra, ev temelli)

- Gözetimsiz ama planlı egzersiz
- Takip vizitleri ile program güncellemesi
- Yıllık izlem [29]

Şekil 2. Kardiyak Rehabilitasyonun Basamakları



Direnç (Ağırlık) Egzersizlerinin Yeri

Uzun süreli olarak sadece aerobik egzersiz değil, direnç egzersizleri de önerilmektedir.

- **Frekans**: Haftada 2–3 gün
- **Setler**: Her büyük kas grubu için 1–3 set
- **Yoğunluk**: 8–12 tekrar ile maksimumun %40–60'ı

Kalp yetersizliği, hipertansiyon, post-MI bireylerde dikkatli başlanmalıdır.

Giyilebilir Teknolojilerin Rolü

- Akıllı saatler ve kalp atım monitörleri sayesinde:
  - Nabız kontrolü
  - Egzersiz süresi ve yoğunluk takibi
  - Düzensiz ritim (AF) bildirimleri
- Kardiyak rehabilitasyona uyumu artırır
- Mobil uygulamalarla eğitim ve motivasyon sağlanabilir

Riskli Durumlar ve Egzersizin Kesilme Kriterleri

Aşağıdaki bulgular egzersizin kesilmesini ve yeniden değerlendirilmesini gerektirir:

- Göğüs ağrısı
- Düzensiz veya hızlı nabız hissi
- Baş dönmesi, senkop
- Hipotansiyon (sistolik <90 mmHg)

- Egzersiz sonrası aşırı yorgunluk, nefes darlığı (NYHA II üstü)

Sonuç olarak kardiyoprotektif egzersiz, yalnızca tedavi değil, aynı zamanda önleyici bir tıbbi yaklaşımdır. Doğru reçetelendirme ve düzenli izlemle kardiyak fonksiyonlar, metabolik parametreler ve yaşam kalitesi anlamlı şekilde iyileşir. FITT prensibi, bireysel risk düzeyine göre yapılandırıldığında etkili ve güvenli bir egzersiz programı sunar.

VIII. SPORCUNUN KLİNİK YÖNETİMİ: MULTİDİSİPLİNER YAKLAŞIM

Sporcuların kardiyovasküler sağlığının yönetimi; yalnızca kardiyologların değil, spor hekimleri, fizyoterapistler, egzersiz fizyologları, antrenörler, psikologlar ve beslenme uzmanlarının birlikte çalışmasını gerektiren dinamik bir süreçtir. Bu multidisipliner yaklaşım, hem tanısal doğruluğu artırır hem de tedavi ve spora dönüş süreçlerini daha güvenli hâle getirir.[30]

Tablo 10. Temel Disiplinler ve Rolleri

Branş / Uzmanlık	**Görev ve Sorumluluklar**
Kardiyolog	Tanı koyar, risk sınıflandırması yapar, tedavi düzenler, spora dönüş kararını verir

Spor Hekimi	Fiziksel uygunluğu değerlendirir, spora katılım formunu onaylar, genel sağlık izlemi yapar
Egzersiz Fizyoloğu	Egzersiz testi uygular, program hazırlar, adaptasyonu izler
Fizyoterapist	Fonksiyonel kapasiteyi artırmaya yönelik bireysel egzersizler planlar
Beslenme Uzmanı	Sporcuya özel diyet planı oluşturur, elektrolit dengesi ve metabolik destek sağlar
Psikolog	Performans anksiyetesi, uyum sorunları ve motivasyon yönetiminde destek sağlar
Antrenör	Egzersiz programını günlük rutine uygular, gözlemsel geribildirim sağlar

Klinik Karar Sürecinde İş birliği Modeli

Sporcuların değerlendirilmesi ve yönetimi, adım adım bir iş akışıyla ilerlemelidir:

1. **Başvuru:** Sporcuda semptom ya da tarama sonucu şüpheli bulgu
2. **Ön Değerlendirme:** Spor hekimi + kardiyolog
3. **Tanı Testleri:** EKG, EKO, CPET, MR, Holter, kan testleri

4. **Multidisipliner Değerlendirme:** Haftalık klinik toplantı, vaka kurul
5. Egzersiz Reçetesi / Kısıtlama Kararı: Tüm branşların ortak onayıyla
6. **İzlem ve Güncelleme:** Aylık kontrol, gerektiğinde program revizyonu

Örnek Vaka Senaryoları

Senaryo 1: Asemptomatik Sporcu, EKG'de Ters T Dalgalı

- Spor hekimi → EKG değerlendirmesi sonrası kardiyolojiye yönlendirir
- Kardiyolog → Ekokardiyografi ve MR ister
- Kardiyak MR'da LGE negatif, kavite normal → patolojik değil
- Egzersiz fizyoloğu → Aerobik yüklenme planı yapar
- Spora dönüş onaylanır → Antrenör ile iletişim kurulur

Senaryo 2: Genç Sporcu, Eforla Çarpıntı Şikâyeti

- Kardiyolog → Holter ve CPET planlar
- Holter: Non-sustained VT → MR ile yapısal inceleme
- MR: ARVC lehine bulgular
- Tanı: ARVC → Spor kısıtlaması getirilir
- Psikolog ve sosyal destek ekibi devreye girer
- Alternatif fiziksel aktiviteler için fizyoterapist ile planlama yapılır

Spor Kulüplerinde Uygulanan Pratik Model

Büyük spor kulüpleri ve elit performans merkezlerinde aşağıdaki model başarıyla uygulanmaktadır:

- Haftalık multidisipliner sporcu sağlığı toplantısı
- Klinik karar defteri ve sporcunun imzasıyla "bilgilendirilmiş karar modeli"
- Antrenör ve sağlık ekibi arasında direkt iletişim hattı
- Tüm test sonuçlarının merkezi bir elektronik sağlık dosyasında toplanması

İletişim ve Eğitim

- **Sporcunun bilgilendirilmesi**: Tanı, tedavi, risk ve spora dönüş süreci ayrıntılı anlatılmalı
- **Aile/velinin katılımı** (özellikle genç sporcularda) sağlanmalı
- **Eğitim materyalleri**: Kendi hastalığını tanıyan ve egzersiz sınırlarını bilen sporcu, tedaviye daha iyi uyum sağlar
- **Antrenör eğitimi**: Aritmi semptomları, efor sınırları, ilaç yan etkileri hakkında bilgilendirilmeli

Sonuç olarak sporcularda kardiyak sorunların yönetimi yalnızca tanı ve tedaviden ibaret değildir. Bu sürecin her adımında multidisipliner ekip iş birliği, sporcunun güvenliği ve performansını birlikte optimize eder. Etkili iletişim, bireyselleştirilmiş programlar ve düzenli izlem, başarılı bir spor kardiyolojisi pratiğinin temel yapı taşlarıdır.

IX. GELECEĞE BAKIŞ VE ARAŞTIRMA ALANLARI

Spor kardiyolojisi, hem tanı teknolojileri hem de kişiye özgü risk analizi yaklaşımları sayesinde hızla evrilen bir alandır. Yapay zekâ destekli karar sistemleri, giyilebilir cihazlarla elde edilen büyük veri, genetik tarama ve kardiyogenomik bilgiler bu alanı ileriye taşıyan başlıca unsurlardır. Önümüzdeki on yıl içerisinde, sporculara yönelik kardiyovasküler risk değerlendirmesi çok daha hassas, kişiselleştirilmiş ve önleyici odaklı olacaktır.[31]

Yapay Zekâ (AI) ve Makine Öğrenimi

a. EKG ve Görüntüleme Yorumunda AI

- AI algoritmaları, klasik yöntemlerin kaçırdığı düşük riskli aritmileri veya preklinik yapısal anomalileri saptamada umut vaat etmektedir.
- Derin öğrenme temelli sistemler, EKG'lerde P dalga morfolojisi, QT varyasyonu, T dalga asimetrisi gibi detaylarda otomatik analiz yapabilir.[32]

b. Karar Destek Sistemleri

- AI destekli klinik karar sistemleri, risk skorlama, tanı koyma ve spora dönüş kararlarında yardımcı olabilir.
- Mevcut sistemler, hastanın yaşı, EF değeri, MR bulguları, CPET sonuçlarını entegre ederek klinisyenlere önerilerde bulunabilir.

Genetik Tarama ve Kardiyogenomik

a. Genetik Yatkınlık

- HCM, ARVC, LQTS gibi hastalıklarda spesifik gen mutasyonları tanımlanmıştır.

- Sporcularda bu mutasyonların taranması, özellikle aile öyküsü olanlarda tanı ve risk sınıflamasını kolaylaştırır.[33]

b. Sporcuya Özgü Genetik Profilleme

- VO_2 max, laktat eşiği, miyokardiyal hipertrofiye yatkınlık gibi özelliklerde rol oynayan genetik polimorfizmler araştırılmaktadır.
- Gelecekte egzersiz reçeteleri, sadece klinik değil, genetik profil temelinde de özelleştirilebilir.

c. Genomik Etik

- Genetik bilginin kullanımı, sigorta, sporcu sözleşmeleri ve etik alanlarda tartışmaları beraberinde getirmektedir.
- "Genetik doping" ve genom düzenleme (CRISPR) gibi ileri uygulamaların sporun doğasına etkileri tartışma konusudur.

Giyilebilir Teknolojiler ve Uzaktan İzlem

- Akıllı saatler ve giyilebilir EKG cihazları, aritmi izlemi ve egzersiz yüklenmesinin takibi için yaygınlaşmaktadır.
- AF, PVC, bradikardi gibi ritim bozukluklarını gerçek zamanlı bildirebilen sistemler geliştirilmiştir.
- Uzaktan CPET, mobil telefon tabanlı Holter ve AI destekli uyku-ritim korelasyonu gibi uygulamalar klinik pratiğe girmektedir.[34]

Büyük Veri ve Dijital Sağlık Kayıtları

- Milyonlarca sporcunun egzersiz, ritim, metabolik verilerinin birleştiği veritabanları oluşturulmaktadır.
- Bu veriler, sporcularda ani kardiyak ölüm riskini öngörmek ve yeni tarama algoritmaları geliştirmek için kullanılabilir.

Egzersiz Omikleri

- Metabolomik, transkriptomik, epigenetik analizlerle egzersizin hücresel ve moleküler etkileri detaylandırılmaktadır.
- Örneğin: Yoğun egzersiz sonrası IL-6, TNF-alfa gen ekspresyon profilleri; antiinflamatuvar etkiler
- Sporcuların inflamatuvar yanıt profilleri, egzersiz tipi ve süresi açısından özelleştirilebilir hâle gelecektir.[35]

Gelecekte Araştırma Öncelikleri

- Ani kardiyak ölüm riskini öngören multimodal prediktif modeller
- Sporcuda "gri bölge" hipertrofi / aritmi ayrımını yapabilen biyobelirteçler
- Kadın sporcularda kardiyovasküler risklerin tanımlanması (bugüne kadar erkek ağırlıklı çalışılmıştır)
- Egzersiz ve kalp yetmezliği ilişkisi: Hangi düzeyde, hangi hasta grubu fayda görür?

Spor kardiyolojisi, yalnızca klinik deneyimle sınırlı kalmayıp, yapay zekâ, genomik analiz ve mobil sağlık

teknolojileriyle evrilen çok disiplinli bir bilim dalı hâline gelmektedir. Önümüzdeki yıllarda, "kişiselleştirilmiş egzersiz kardiyolojisi" anlayışı daha ön planda olacak; bireyin genetik yapısı, dijital verileri ve fizyolojik kapasitesi birlikte değerlendirilerek hem güvenli hem de performansa uygun spor planlaması yapılabilecektir.

X. SONUÇ VE KLİNİK ÖNERİLER

Genel Değerlendirme

Spor kardiyolojisi, sadece elit sporcuların değil, her yaş ve seviyeden fiziksel olarak aktif bireylerin güvenliğini sağlamak açısından büyük önem taşımaktadır. Egzersizin kardiyovasküler sistem üzerindeki olumlu etkileri tartışmasızdır; ancak bireysel risk faktörlerinin göz ardı edilmesi, nadir de olsa ciddi komplikasyonlara yol açabilir. Bu nedenle, sporcunun kalbi fizyolojik adaptasyonla patolojinin ayırt edilebildiği, tanı, risk sınıflandırması ve spora dönüş kararlarının disiplinler arası yaklaşımla verildiği bir çerçeveye ihtiyaç vardır.

Son yıllarda rehberler, teknoloji, görüntüleme, genetik tarama ve yapay zekâ gibi yeniliklerle bu alanda önemli ilerlemeler sağlanmıştır. Ancak tüm bu araçların doğru kullanımı, ancak sahaya yakın, klinik deneyimi yüksek multidisipliner ekiplerle mümkündür.

Klinik Öneriler

Tanı ve Tarama

- Egzersize katılacak bireylerde temel kardiyolojik tarama (anlamlı öykü, EKG, fizik muayene) en az bir kez yapılmalıdır.
- Şüpheli EKG veya semptomatik bireylerde ileri tetkikler (EKO, MR, Holter, CPET) gereklidir.

- Genç sporcularda ani ölüm nedenleri genetik/konjenital hastalıklar; erişkinlerde ise KAH kaynaklıdır – tarama buna göre planlanmalıdır.
- "Atlet kalbi" ile patoloji ayırımı mutlaka yapılmalı, gri bölgelerde ek testler kullanılmalıdır.

Risk Sınıflaması ve Spora Dönüş

- Kardiyovasküler hastalık öyküsü olan bireylerde spora dönüş, sadece EF veya semptomlarla değil, MR, aritmi analizi, CPET gibi çoklu parametrelerle değerlendirilmelidir.
- Spora dönüş kararları, mümkünse multidisipliner kurulda verilmeli ve hasta bilgilendirilerek imzalı "ortak karar" formu kullanılmalıdır.
- Miyokardit, ARVC ve aktif aritmiler varlığında spora kesin kısıtlama getirilmelidir.

Egzersiz Planlaması

- FITT prensibiyle bireyselleştirilmiş egzersiz reçetesi verilmelidir.
- Direnç egzersizleri aerobik programlara entegre edilmelidir.
- Yüksek riskli bireylerde egzersiz gözetimli olarak, tercihen kardiyak rehabilitasyon programı içinde uygulanmalıdır.

Multidisipliner Yaklaşım

- Kardiyolog, spor hekimi, fizyoterapist, egzersiz fizyoloğu, beslenme uzmanı ve antrenör ekip halinde çalışmalıdır.

- Eğitim materyalleriyle hasta ve ailesi sürece aktif olarak dâhil edilmelidir.

Geleceğe Hazırlık

- Genetik analiz, yapay zekâ, giyilebilir teknolojiler gibi yeni araçlar dikkatli ve etik temellerle entegre edilmelidir.
- Kadın sporcular, genç bireyler, cihazlı hastalar gibi özel gruplar için ayrı protokoller oluşturulmalıdır.

Anahtar Mesajlar

- Her sporcu potansiyel olarak yüksek performanslı bir fizyolojik sistem taşırken, aynı zamanda sessiz bir risk de taşıyabilir.
- Doğru kararlar, deneyimli ekiplerle ve ortak akılla verildiğinde güvenli ve sürdürülebilir spor mümkün olur.
- Egzersiz, reçetelendirilebilir bir tedavi modalitesidir; dikkatle planlandığında kardiyovasküler sağlığın en güçlü silahıdır.
- Önleme, teşhis ve rehabilitasyonun uyum içinde olduğu bir yapı, spor kardiyolojisinin asıl gücüdür.

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BÖLÜM 2

BAĞIRSAK MİKROBİYOTASININ KARDİYOVASKÜLER HASTALIKLAR ÜZERİNE ETKİSİ

CANAN AYDOĞAN[1]

Giriş

İnsan vücudunda birçok organ ve dokuda kolonize olmuş toplam 1014 mikroorganizma olduğu tahmin edilmektedir. Bu mikroorganizmaların büyük çoğunluğunu bakteriler oluşturmakla birlikte, virüsler, funguslar ve birçok ökaryotik mikroorganizma da mikrobiyotayı oluşturmaktadır. Gastrointestinal sistem yaklaşık 200m² yüzey alanı ve mikroorganizmalar için zengin besin öğeleri içermesi nedeniyle kolonizasyon için en uygun ortamı sağlamaktadır (1).

İnsanlarda intestinal mikrobiyota çok sayıda ve çeşitlilikte mikroorganizma tarafından oluşturulmuş kompleks ve dinamik bir ekosistemdir. Bu ekosistem besin sindirimi, bağışıklık sistemi düzenlenmesi ve metabolik homeostazın sağlanması gibi temel biyolojik süreçlerde önemli rol oynamaktadır (2).

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Son yıllarda, bağırsak mikrobiyotasının insan sağlığı üzerindeki etkileri daha fazla araştırılmaya başlanmış ve çeşitli hastalıkların gelişmesinde kritik bir rol oynadığı anlaşılmıştır. Bir bebek doğmadan önce bağırsağında çok az mikroorganizma vardır (3). Vücut, doğumdan itibaren sürekli olarak dış dünya tarafından uyarılır ve bağırsaktaki mikroorganizmaların sayısı artmaya başlar ve bağırsak mikrobiyotasının dinamik dengesini kademeli olarak oluşturur (4).

Beslenme alışkanlıkları, çevresel faktörler, bağırsak enfeksiyonları veya diğer faktörler yetişkin bağırsağındaki bağırsak mikroorganizmalarının türlerinde ve miktarında değişikliklere yol açar ve bağırsak disbiyozu meydana gelir. Bağırsak disbiyozu iltihaplanmaya, metabolik bozukluklara ve dünya çapında en önemli morbidite ve mortalite nedenlerinden biri olan kardiyovasküler hastalıkların gelişimine neden olur (5). Bu nedenle bağırsak mikrobiyotasını düzenlemeye yönelik tedavi yaklaşımlarının (probiyotikler, prebiyotikler, fekal mikrobiyota transplantasyonu gibi) kardiyovasküler hastalık riskini azaltmada umut vadettiği düşünülmektedir.

Bağırsak mikrobiyotası ve kardiyovasküler hastalıklar arasındaki ilişki, özellikle metabolik ürünlerin vasküler sistem üzerindeki etkileri üzerinden şekillenmektedir. Bağırsak bakterileri, diyetle alınan besinleri metabolize ederek çeşitli biyokimyasal bileşenler üretir. Bunların bazıları, kardiyovasküler sağlığı olumlu yönde etkilerken, bazıları ise ateroskleroz, hipertansiyon ve diğer kardiyovasküler risk faktörlerine katkıda bulunabilir. Özellikle trimetilamin (TMA), trimetilamin-N-oksit (TMAO), kısa zincirli yağ asitleri (SCFA) ve lipopolisakkaritler (LPS) gibi bağırsak mikrobiyatası tarafından üretilen metabolitlerin kardiyovasküler hastalıkların patofizyolojisinde önemli rol oynadığı gösterilmiştir (6).

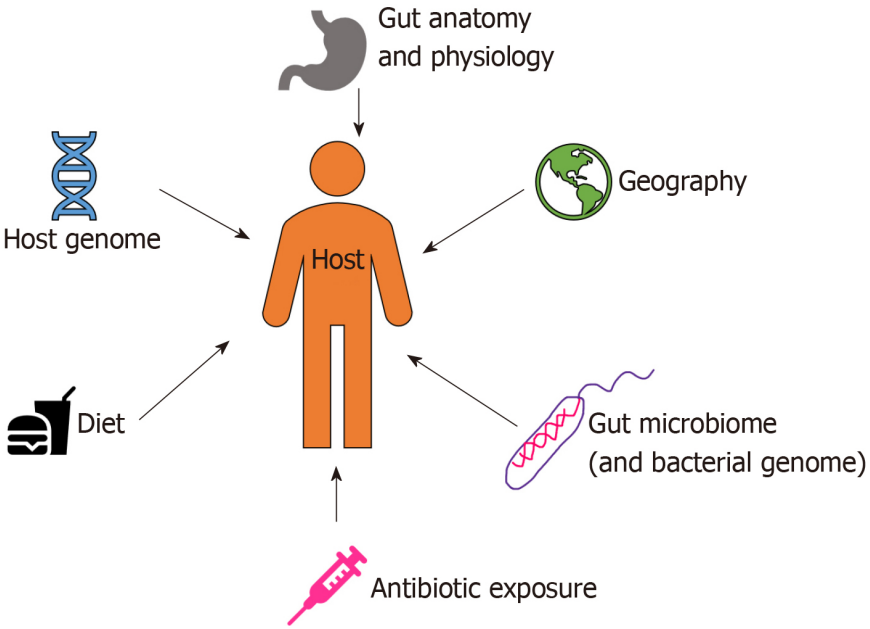
Bu bölüm, bağırsak mikrobiyotası ile kardiyovasküler hastalıklar arasındaki etkileşimleri detaylı bir şekilde incelemeyi amaçlamaktadır. Öncelikle bağırsak mikrobiyotasının genel yapısı ve işlevleri ele alınacak, ardından mikrobiyal metabolitlerin kardiyovasküler sağlık üzerindeki etkileri tartışılacaktır. Son olarak, bağırsak mikrobiyotasını düzenlemeye yönelik tedavi yaklaşımları ve gelecekteki araştırma perspektifleri değerlendirilecektir.

Bağırsak Mikrobiyotasının Yapısı ve Fonksiyonları

Bağırsak mikrobiyotası, insan bağırsaklarında yaşayan trilyonlarca mikroorganizmadan oluşan bir ekosistemdir. Mikrobiyal gen havuzunun insan genomundan daha büyük olduğu gösterilmiş ve bu durum "metagenom" olarak adlandırılmıştır (7). Mikrobiyal türlerin %90'ını Firmicutes ve Bacteroidetes oluştururken geri kalanını Actinobacteria, Cyanobacteria, Fusobacteria, Proteobacteria ve Verrucomicrobia oluşturmaktadır (8-9).

Bağırsak mikrobiyotasının bileşimi, bireyler arasında büyük farklılıklar gösterebilir ve birçok faktörden etkilenebilir. Genetik yapı, beslenme alışkanlıkları, yaş, çevresel faktörler ve kullanılan ilaçlar (özellikle antibiyotikler) mikrobiyota çeşitliliğini ve dengesini belirleyen önemli faktörlerdir (Şekil 1) (10).

Şekil 1 Bağırsak Mikrobiyatasının Gelişimini Etkileyen Faktörler

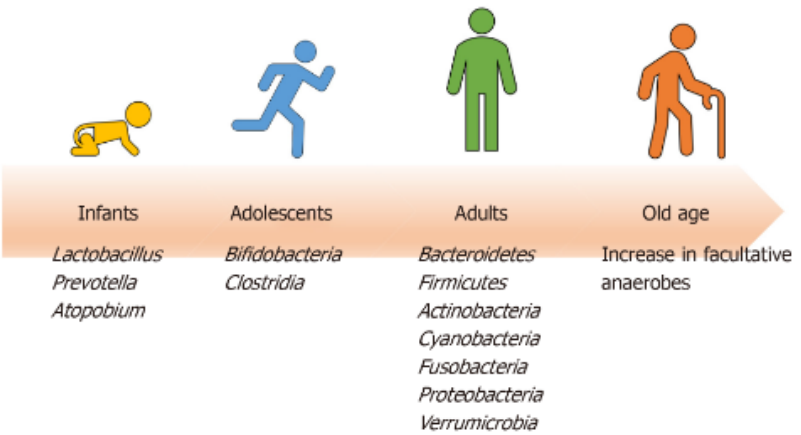


Perinatal dönemde (doğum öncesi ve doğum sonrası dönem) anne florası, doğum yöntemi, emzirme ve sütten kesilme süreci mikrobiyom gelişimini etkilemektedir. Özellikle vajinal doğumla dünyaya gelen bebeklerin bağırsak mikrobiyotası ağırlıklı olarak Lactobacillus, Prevotella ve Atopobium türlerini içerirken, sezaryenle doğan bebeklerin bağırsaklarında ağırlıklı olarak annelerinin deri florasında bulunan Staphylococcus bakterileri yer almaktadır (11). Bebek büyüdükçe, bağırsakta bulunan aerobik mikroorganizmalar çeşitlenerek anaerobik bir ortam oluşturmaktadır. Ergenlerde Bifidobacteria ve Clostridia oranlarının yetişkinlere kıyasla daha yüksek olduğu gözlemlenmiştir.

İlginç bir şekilde, bağırsak mikrobiyotası yaşla birlikte evrim geçirdikçe bağırsaktaki metabolik ortam da değişmektedir. Yetişkinlik boyunca bağırsak mikrobiyotasının bileşiminin büyük ölçüde sabit kaldığı görülmüştür. Bununla birlikte, yaşlanmayla

birlikte fizyolojik fonksiyonların gerilemesine bağlı olarak bazı değişiklikler meydana gelmektedir (Şekil 2) Bağışıklık sisteminin zayıflamasıyla birlikte fakültatif anaerop bakterilerin sayısında artış, Bacteroidetes ve Firmicutes oranında değişiklikler ve Bifidobacteria seviyelerinde belirgin bir azalma görülmektedir (12).

Şekil 2 Yaşla Birlikte Bağırsak Mikrobiyotasının Evrimi



Bağırsak mikrobiyotası, hem sağlıklı bireylerde hem de hastalarda önemli işlevlere sahiptir. Bu mikroorganizmalar, besinlerin sindirilmesi, vitamin sentezi ve immün sistemin düzenlemesi gibi çeşitli fonksiyonlara sahiptir. Ayrıca, bağırsak epitel hücreleriyle etkileşime girerek bağırsakların bariyer fonksiyonunu da desteklemektedir. (13-14). Bağırsak duvarındaki sızıntılar aracılığıyla mikrobiyomun bileşenleri bağışıklık sistemi ile sürekli olarak etkileşime girer. Bu etkileşim bağışıklık sisteminin şekillenmesine yardımcı olur ve bağışıklık sistemi de buna karşılık bağırsak mikrobiyotasını değiştirebilir. Sağlıklı bir bağırsak mikrobiyotası, patojenik mikroorganizmaların aşırı çoğalmasını önleyerek ve bağışıklık sistemini destekleyerek konakçının genel sağlığını korumaya yardımcı olur (15).

Bağırsak mikrobiyotası, bağırsak-beyin ekseni ve bağırsak-kalp ekseni gibi sistemler üzerinden vücudun diğer bölgeleriyle de etkileşim halindedir (16-17) Örneğin, bağırsak mikrobiyotası tarafından üretilen bazı metabolitler, sinir sistemi fonksiyonlarını etkileyerek nörolojik hastalıklarla ilişkilendirilebileceği gibi (18), vasküler fonksiyonları düzenleyerek kardiyovasküler hastalık riskini de değiştirebilir (19). Mikrobiyal çeşitlilikteki azalma, yani disbiyozis, bağışıklık sisteminin aşırı aktivasyonuna ve kronik enflamasyona neden olarak çeşitli hastalıkların gelişimini tetikleyebilir (20-21).

Bağırsak mikrobiyotası ayrıca bağırsak bariyer fonksiyonunu da doğrudan etkiler (22). Sağlıklı bir bağırsak mikrobiyotası, bağırsak epitel hücrelerini ve mukus tabakasını güçlendirerek patojenlerin kana geçişini önler (23). Ancak, bağırsak mikrobiyotasında meydana gelen dengesizlikler, bağırsak geçirgenliğinin artmasına ve zararlı bileşenlerin (örneğin lipopolisakkaritler) dolaşıma karışmasına yol açarak sistemik enflamasyonu artırabilir (24). Bu durum, özellikle kardiyovasküler hastalıkların oluşması açısından önemli bir risk faktörüdür.

Bağırsak mikrobiyotası, aynı zamanda çeşitli biyolojik moleküllerin sentezinde de rol oynar Örneğin, kısa zincirli yağ asitleri (SCFA) gibi metabolitler bağırsak epitel hücreleri tarafından enerji kaynağı olarak kullanılır ve anti-enflamatuar etkiler gösterir. Butirat gibi SCFA'lar, bağırsak epitel hücrelerinin bütünlüğünü koruyarak bağırsak bariyer fonksiyonunun sürdürülmesine katkıda bulunur.

Özetle, bağırsak mikrobiyotası, insan sağlığında kritik roller üstlenen, dinamik ve çok yönlü bir ekosistemdir Mikrobiyotanın dengesinin korunması, sadece gastrointestinal sağlığı değil, aynı zamanda kardiyovasküler ve metabolik hastalıkların önlenmesini de destekleyen önemli bir faktördür (25).

Bağırsak Mikrobiyotasının Kardiyovasküler Sağlıkla İlişkisi

Bağırsak mikrobiyotası, kardiyovasküler sağlığı doğrudan ve dolaylı olarak etkileyen bir dizi mekanizmaya sahiptir. Mikrobiyota kaynaklı metabolitler; inflamasyon süreçleri, immün yanıt ve vasküler homeostaz üzerinde belirleyici roller üstlenmektedir. Özellikle bağırsak mikrobiyotasının ürettiği bazı metabolitler, arteriyel sertleşme, hipertansiyon ve dislipidemi gibi kardiyovasküler hastalıklarla doğrudan ilişkilendirilmiştir (26).

Mikrobiyal Metabolitler ve Kardiyovasküler Hastalıklar

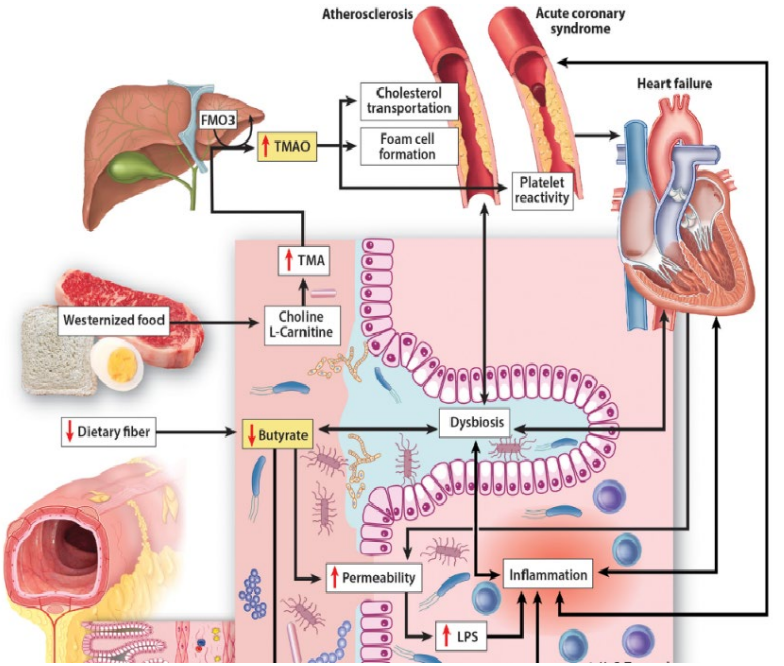
Bağırsak bakterileri tarafından sentezlenen metabolitler, kardiyovasküler sağlık üzerinde çeşitli etkiler oluşturabilir. Bu metabolitler şunlardır.

Trimetilamin N-oksit (TMAO): Kırmızı et ve diğer hayvansal gıdalardan elde edilen kolin ve L-karnitin, bağırsak bakterileri tarafından metabolize edilerek trimetilamin (TMA) oluşturur. TMA, karaciğerde trimetilamin Noksit (TMAO)'e dönüşür. TMAO proaterojenık ve protrombotiktir. ateroskleroz ile ilişkili bulunmuştur (27). Artan TMAO seviyeleri, tromboz riskini yükseltirken, endotelyal disfonksiyon ve damar sertliği gibi faktörleri de tetikleyebilir.

Kısa Zincirli Yağ Asitleri (SCFA'lar): Butirat, asetat ve propionat gibi SCFA'lar, inflamasyonu baskılayarak, insülin duyarlılığını artırarak ve bağırsak bariyer fonksiyonlarını geliştirerek kardiyovasküler hastalık riskini azaltabilir (28).

Lipopolisakkaritler (LPS): Gram-negatif bakterilerin hücre duvarında bulunan LPS, sistemik inflamasyonu tetikleyerek endotelyal disfonksiyon ve ateroskleroza katkı sağlayabilir (29).

Şekil 5 Mikrobiyota ve Kardiyovasküler Sistem Üzerine Etkisi (29)



Mikrobiyota ve Hipertansiyon

Bağırsak mikrobiyotasının bileşimi ve metabolitleri, kan basıncı düzenlenmesinde kritik rol oynar. Gram-negatif mikrobiyota bolluğu (Klebsiella, Parabacteroides, Desulfovibrio ve Prevotella gibi türlerin fazla oranda bulunması) yüksek kan basıncı ile ilişkilendirilmiştir Buna karşılık, Ruminococcaceae, Roseburia ve Faecalibacterium gibi SCFA üreten bakterilerin, hipertansif hastalarda normotansif hastalara kıyasla daha az olduğu gösterilmiştir. (30)

İntestinal bakterilerin ürettiği aromatik-L-amino asit dekarboksilaz ile tirozin tiramine dönüşür. Lactobacillus bulgaricus; histamin, tiramin ve triptamin, Enterococcus faecalis; tiramin, Lactobacillus plantarum; histamin ve tiramin üretirler. Esansiyel hipertansiyon etiyopatogenezinden mikrobiyata disbiyozisi sonucu

oluşan tiraminin aşırı üretiminin sorumlu olabileceği düşünülmektedir. Mikrobiyotanın disbiyotik bir hale gelmesiyle bağırsak geçirgenliğinin artması, inflamatuar yanıtların tetiklenmesi ve bu süreçlerin vasküler direnci artırarak kan basıncının yükselmesine neden olduğu gösterilmiştir (31).Ayrıca böbrek ve kan damarlarının düz kas hücrelerinde bulunan SCFA reseptörlerinin (chemosensor olfactory receptor 78 (OLFR78) ve GPR41) renin-aldosteron sistemi üzerinden kan basıncını etkilediği gösterilmiştir (32).

Mikrobiyota ve Dislipidemi

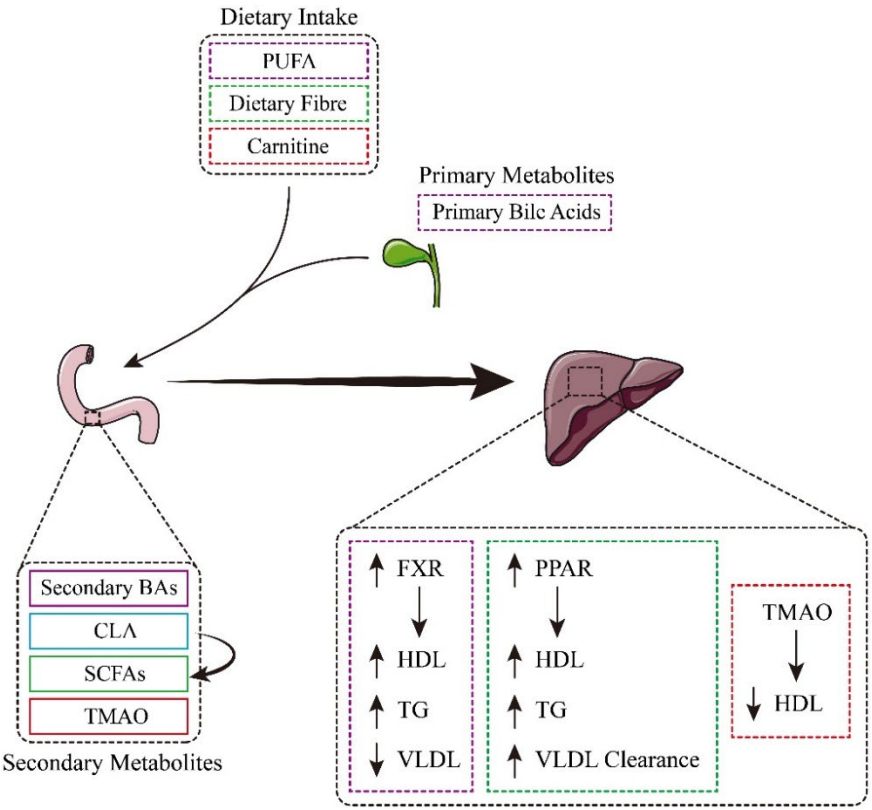
Bağırsak mikrobiyotasındaki değişim dislipideminin oluşumu ve gelişimiyle yakından ilişkilidir. Yüksek yağlı diyet veya dislipidemi, bağırsak mikrobiyotasının bağlı olduğu bağırsak ortamını değiştirebilir, bağırsağın normal florasının üremesini ve metabolizmasını etkileyerek bağırsak mikrobiyotasının dengesizliğine yol açabilir. Buna bağlı olarak lipid metabolizması bozuklukları ağırlaşır ve bir kısır döngü oluşur.

Bağırsak ortamı değiştiğinde, Bifidobacterium, Lactobacillus ve bütirik asit üreten bakteriler gibi normal floraların üremesi baskılanır, Enterobacteria ise artar ve bu düzensizlik dislipidemiye yol açar. Buna karşılık, dislipidemi bağırsak mikrobiyotasındaki dengesizliği daha da kötüleştirir. Vücuda alınan çoklu doymamış yağ asitleri (PUFA), diyet lifi, karnitin ve safra asitleri gibi birçok besin, sindirim sırasında mikrobiyal enzimler tarafından parçalanarak kısa zincirli yağ asitleri (SCFA'lar), konjuge linoleik asit (CLA), trimetilamin N-oksit (TMAO) ve ikincil safra asitleri üretir. CLA üretimi, SCFA'ların oluşumunu teşvik edebilir ve dolaylı olarak SCFA'ların genel verimini etkileyebilir.

Bağırsakta üretilen ikincil metabolitler vücudun farklı bölgelerinde rol oynar. Örneğin, karaciğerde TMAO, HDL'yi

azaltarak lipid metabolik dengesini bozar. SCFA'lar ve CLA, peroksizom proliferatör-aktifleşmiş reseptörler (PPAR'lar) ile etkileşime girerek yüksek seviyelerdeki HDL, trigliserit (TG) ve VLDL' yi temziler. Ayrıca, ikincil safra asitlerinin FXR reseptörleriyle etkileşimi, yüksek HDL ve lipoliz ile düşük seviyede VLDL ile ilişkilidir (şekil 3) (33).

Şekil 3 Diyet, Bağırsak Mikrobiyotası ve Lipid Metabolizması Arasındaki Etkileşim



Genel olarak diyet, bağırsak mikrobiyotasının bileşimini etkileyen en önemli faktördür. Bağırsak mikrobiyotası, besin miktarına ve bileşimine duyarlıdır.

Bağırsak mikrobiyotası, kolesterol oksidaz üreterek kolesterol sentezini inhibe eder ve kolesterolün yıkımını ve dönüşümünü teşvik ederek dislipidemide önemli rol oynar. Bağırsak mikrobiyotası, konak enerji metabolizması ve bağırsak epitel geçirgenliğini değiştirerek , bağırsak peptid hormon sekresyonu ve konak iltihaplanma durumu gibi birçok yolu düzenleyerek bağırsak homeostazını bozar, safra asidi metabolizmasını anormal hale getirir ve kısa zincirli yağ asitlerinin bileşimini ve üretimini değiştirerek dislipidemiye neden olur (34-35).

Yüksek protein ve karbonhidrat ile beslenen kişilerde ortaya çıkan parçalanmamış polisakkaritler mikrobiyota ile fermantasyona uğramaktadır. Fermantasyon sonucu oluşan Kısa zincirli yağ asitleri bağırsak epitel hücrelerinin duvarındaki iki çeşit G proteinine bağımlı reseptörü (GPR41 ve GPR43) aktifler. GPR41'inin aktiflenmesi; leptin seviyesinin artmasına, nöropeptit Y'nin azalmasına ve GLP-1 artışına, GPR43'ün aktiflenmesi ise; propionat ve asetat üzerinden adipogenezin artmasına neden olmaktadır(36)

Fu ve Arkadaşlarının yaptığı çalışmada Firmicutes ve Bacteroides'in kan lipid seviyelerindeki değişiklikleri etkileyen ana bakteriyel filumlar olduğu ve serum trigliserit ve yüksek yoğunluklu lipoprotein kolesterol seviyeleri üzerinde büyük etkileri olduğu ortaya çıkmıştır (37-38)

Bağırsak mikrobiyotası genetik, yaşam tarzı, diyet, antibiyotik tedavisi ve diğer faktörlerden etkilenir. Umair ve Arkadaşları, 16S rRNA gen sekanslama yöntemini kullanarak, yüksek yağlı diyetin kolondaki Firmicutes ve Bacteroidetes oranını önemli ölçüde artırabileceğini, yüksek yağlı et proteininin ise serumdaki Bifidobakterilerin kısmi bolluğunu önemli ölçüde azaltırken lipopolisakkarit seviyesini artırabileceğini, endojen kannabinoid reseptör dengesizliğine yol açarak adipogenezi teşvik edebileceğini göstermiştir Bu nedenle, diyet alışkanlıklarını

iyileştirmek ve spesifik ilaçlarla düzenlemek dislipidemi ve aterosklerozun önlenmesi ve tedavisi için bir stratejidir (39).

Sonuç olarak, çok sayıda hayvan modeli ve insan çalışması, bağırsak mikrobiyotasındaki bozulmanın dislipideminin önemli bir nedeni olduğunu tekrar tekrar göstermiştir. Yüksek yağlı diyete bağlı dislipidemi için bağırsak mikrobiyotasının düzenlenmesi yeni bir tedavi yaklaşımı olabilir.

Mikrobiyota ve Ateroskleroz

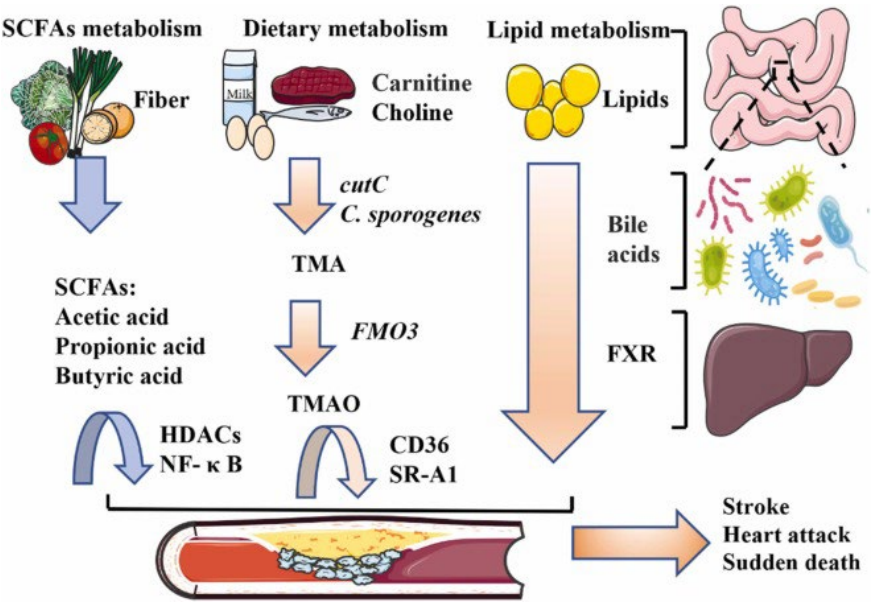
Bağırsak mikrobiyomu, metabolik enzimler ve ürünler aracılığıyla kardiyovasküler sağlık üzerinde önemli bir etkiye sahiptir. Mikrobiyotadaki mikroorganizmaların prosklerotik veya antisklerotik özellikleri, bu etkileşimin temelini oluşturur. Ayrıca, mikroorganizma oranlarının dengesi de bu etkileşimde önemli rol oynar.

Bağırsak mikrobiyomu, endokrin bir organ gibi davranarak, ateroskleroz üzerinde etki eder. Bağırsak mikrobiyomunun bu etkisi, iki ana yol aracılığıyla açıklanabilir. Birincisi, TMAO, safra asitleri ve aromatik aminoasitlerin metabolitlerinin aterosklerozu tetikleyici etkisi; diğeri ise kısa zincirli aminoasitler ve poliaminlerin ateroskleroza karşı koruyucu etkisidir (40).

Diyetteki sebze lifleri bağırsak mikrobiyomu tarafından kısa zincirli yağ asitlerine (asetik asit, propiyonik asit ve bütirik asit) dönüştürülür; SCFA'lar, histon deasetilazlarını (HDAC'ler) inhibe ederek ve NF-κB'nin aktive olmasını azaltarak ateroskleroza karşı koruyucu etki eder. İkinci olarak, diyetteki karnitin veya kolin kaynakları bağırsakta C.sporogenes'in cutC enzimi tarafından TMA'ya dönüştürülür. TMA, portal dolaşıma geçer ve karaciğerde monoamin oksidaz 3 (FMO3) tarafından daha da oksitlenerek TMAO'yu üretir. TMAO, plak oluşumunu artırarak aterosklerozun oluşumunu ve prognozunu etkiler. Son olarak, lipitler bağırsak mikrobiyomu tarafından safra asidi metabolizması ve karaciğerin

FXR'si aracılığıyla ateroskleroz gelişimini etkileyebilir. Aterosklerotik plak yırtıldığında, felç, kalp krizi ve ani ölüm meydana gelebilir (şekil 4) (41)

Şekil 4 Trimetilaminoksit, Kısa Zincirli Yağ Asitlerin ve Farnezoid X Reseptörünün Kardiyovasküler Hastalıklar Üzerine Etki Mekanizmaları



Ateroskleroz, genellikle çocukluk ve gençlik yıllarında başlar ve zamanla damarların iç duvarlarında plak oluşumuna yol açarak ilerler. Bu plaklar damarları daraltır ve iltihaplanmaya neden olabilir, bu da daha fazla plak oluşumunu tetikler. Metagenomik analizler, aterosklerozlu bireylerde belirli bakteri türlerinin yoğunluğunun arttığını ve bunun damar hastalığının şiddetiyle de ilişkili olduğunu göstermiştir. Örneğin, Firmicutes/Bacteroidetes oranı, aterosklerozlu hastalarda sağlıklı bireylere göre daha yüksektir. Ayrıca, sağlıklı bireylere kıyasla aterosklerozu olan

kişilerde Chryseomonas ve Helicobacter türlerinin düzeyleri de daha yüksek bulunmuştur.

Ateroskleroz patogenezinde önemli bir rol oynayan mikroorganizmalar arasında Akkermansia Muciniphila öne çıkmaktadır. Ayrıca, bazı bakterilerin aterosklerotık kardiyovasküler hastalıkların saptanmasında biyomarker olarak kullanılabileceği yönünde araştırmalar mevcuttur. Bu araştırmalara göre Bacteroidetes'in yüksek konsantrasyonda bulunması ve Prevotella ve Bacteroides cinslerinin düşük konsantrasyonda bulunması kardiyovasküler hastalıklar için potansiyel biyomarker olduğu gösterilmiştir (42).

Mikrobiyota Kardiyomiyopati ve Kalp Yetersizliği

Kalp yetmezliği; dispne, alt ekstremite ödemi, azalmış efor kapasitesi gibi tipik semptomların bir arada görüldüğü bir durumdur ve bu semptomlar, fiziksel muayenelerdeki anormalliklerle (örneğin, juguler venlerin genişlemesi, akciğerlerde hışırtı, periferik ödem) birlikte olabilir(43).

Kalp yetmezliği kalp yapısındaki ve fonksiyonundaki anormalliklerle, dinlenme veya egzersiz sırasında azalmış kardiyak debi ve/veya artmış intrakardiyak basınç nedeniyle ortaya çıkar. Kalp yetersizliğinin, gelişmiş ülkelerdeki yetişkin nüfusun %1–2'sini etkilediği tahmin edilmektedir (44)

Son dönemde, kalp yetmezliğinin patogenezindeki bağırsak mikrobiyotasının rolüyle ilgili bir kavram ortaya çıkmıştır; bu "kalp yetmezliğinin bağırsak hipotezi" olarak adlandırılmaktadır. Bu hipoteze göre, sistemik konjesyonun artışı ve kalp debisinin azalması, bakterilerin translokasyonunda artışa neden olarak dolaşımdaki toksinlerin artışına yol açar; bu da kalp yetmezliği olan hastalarda enflamasyonun temel nedenidir.(45-46). Kalp debisinin azalmasıyla oluşan bağırsak hiperfüzyonu, bağırsak mukozasında iskemi veya ödemle sonuçlanır, bu da bariyer işlevinin bozulmasına

yol açar ve kalp yetmezliğinin gelişimini ve ilerlemesini şiddetlendirir (47).

Kronik kalp yetmezliği hastalarında, Yersinia Enterocolitica, Campylobacter, Shigella gibi patojenik bakteriler ve Candida gibi bazı fungusların kolonizasyonun başlıca görüldüğü tespit edilmiştir. Bu bakteriyel ve fungal izolatlar, kalp yetmezliğinin şiddeti ile pozitif korelasyon göstermektedir. Ayrıca dekompanse olmuş kalp yetmezliği vakalarında, kompanse kalp yetmezliği olan vakalara göre bu bakterilerin daha fazla bulunduğu görülmüştür (48).

Sağlıklı kontrol grubuna kıyasla, aynı yaş ve cinsiyetteki kalp yetmezliği hastalarında serum TMAO seviyelerinin daha yüksek olduğu bulunmuştur (49) Kalp yetmezliği hastalarında yüksek TMAO seviyeleri, daha yüksek mortalite (~1.18 kat) ve kalp nakli oranları (~1.79 kat) ile ilişkilidir (50). Artmış serum TMAO seviyesi ventriküler remodelingin ve miyokardial fibrozisin artmasına önemli ölçüde katkıda bulunur ve kalp yetmezliği riskinin sınıflandırılmasında prognostik bir belirteç olarak önemli bir değere sahiptir (51).

Klinik ve Terapötik Yaklaşımlar

Bağırsak mikrobiyotasının kardiyovasküler sağlık üzerindeki etkileri göz önüne alındığında, mikrobiyotayı düzenlemeye yönelik çeşitli klinik ve terapötik yaklaşımlar geliştirilmiştir. Probiyotikler ve prebiyotikler, diyet düzenlemeleri ve fekal mikrobiyota transplantasyonu (FMT) gibi stratejiler, kardiyovasküler hastalıkların önlenmesi ve tedavisinde umut vadetmektedir.

Probiyotikler ve Prebiyotikler

Probiyotikler yeterli miktarda alındığında bağırsak mikrobiyotasının dengesini iyileştirmeye yardımcı olan canlı mikroorganizmalardır. Yoğurt, kefir gibi fermente gıdalarda bulunur ve özellikle Lactobacillus ve Bifidobacterium gibi bakteriler ile

Saccharomyces gibi mayaları içerir. Probiyotikler bağışıklık yanıtını güçlendirir, sindirimi kolaylaştırır ve önemli vitaminlerin sentezine katkı sağlar. Ayrıca bağırsak bariyer fonksiyonunu güçlendirerek sistemik inflamasyonu azaltır ve böylece ateroskleroz riskini azaltır. (52).

Prebiyotikler ise sindirilemeyen inülin gibi karbonhidratlar ve oligosakkaritler içeren faydalı mikroorganizmaların büyümesini teşvik eden maddelerdir ve soya fasulyesi, yulaf gibi gıdalarda bulunur. Frukto-oligosakkaritler (FOS), galakto-oligosakkaritler (GOS) ve inülin gibi prebiyotikler, kısa zincirli yağ asitleri üretimini teşvik ederek kardiyovasküler sağlığı olumlu yönde etkileyebilir. Yapılan çalışmalar, prebiyotiklerin kan basıncını düşürdüğünü, inflamatuar belirteçleri azalttığını ve lipid profiline olumlu katkılar sağladığını göstermektedir (53).

Beslenme

Bağırsak mikrobiyotasını düzenlemenin en önemli yollarından biri beslenme alışkanlıklarını değiştirmektir. Akdeniz diyeti; tekli ve çoklu doymamış yağ asitlerinden zengin yağ asidi profili ve yüksek düzeyde polifenol ve antioksidan gibi sağlıklı beslenmeyi içermekte olup bağırsak mikrobiyotasının dengesini korumaya yardımcı olur. Akdeniz diyetine düşük uyum olan kişilerde kardiyovasküler hastalıklar için risk faktörü olan trimetilamin oksit seviyesinde artış belirlenmiştir Çoğu çalışmada Akdeniz diyetinin aynı zamanda obezite, lipid profili ve inflamasyon üzerine de olumlu etkileri olduğu görülmüştür. Ayrıca Akdeniz diyeti ile Lactobacillus, Bifidobacterium ve Prevotella yoğunluğunun arttığı Clostridium yoğunluğunun azaldığı tespit edilmiştir (54).

Buna ek olarak, hayvansal protein açısından zengin diyetlerin bağırsak mikrobiyotasında değişikliklere yol açarak TMAO üretimini artırdığı ve bu durumun ateroskleroz riskini yükselttiği gösterilmiştir. TMAO seviyelerinin düşürülmesi

amacıyla, bitkisel bazlı proteinlerin ve lif içeriği yüksek besinlerin tüketilmesi önerilmektedir (55).

Fekal Mikrobiyota Transplantasyonu

Fekal mikrobiyota transplantasyonu (FMT), bağırsak mikrobiyotasının sağlıklı bireylerden alınıp bozulmuş mikrobiyotaya sahip bireylere transfer edilmesini içeren bir yöntemdir. Bu teknik, özellikle Clostridium difficile enfeksiyonlarının tedavisinde etkili bulunmuş olup, son yıllarda kardiyovasküler hastalıklarla ilişkili metabolik bozuklukların yönetiminde de araştırılmaktadır. FMT' nin bağırsak mikrobiyotasını olumlu yönde değiştirerek sistemik inflamasyonu azalttığı ve metabolik süreçleri iyileştirdiği gösterilmiştir (56).

FMT'nin kardiyovasküler hastalıklar üzerindeki potansiyel faydaları henüz tam olarak kanıtlanmamış olsa da, yapılan bazı çalışmalar FMT'nin kan basıncını düzenleyebileceğini ve metabolik sendrom semptomlarını hafifletebileceğini öne sürmektedir. Ancak bu tedavi yöntemi hala klinik araştırmaların erken aşamalarında olup, uzun vadeli etkileri daha fazla araştırılmalıdır (57).

Sonuç

Bağırsak mikrobiyotası, kardiyovasküler sağlık üzerinde çok yönlü etkiler oluşturan kritik bir bileşendir. Mikrobiyota bileşiminin ve işlevlerinin, inflamasyon, lipid metabolizması, kan basıncı regülasyonu ve bağışıklık sistemi üzerinde doğrudan etkileri olduğu gösterilmiştir. Özellikle bağırsak bakterileri tarafından üretilen metabolitler, kardiyovasküler hastalıkların patofizyolojisinde önemli roller oynayarak, ateroskleroz, hipertansiyon, kalp yetmezliği ve dislipidemi gibi durumların gelişmesine katkıda bulunabilir.

Bu nedenle, bağırsak mikrobiyotasının düzenlenmesi, kardiyovasküler hastalıkların önlenmesi ve tedavisinde önemli bir hedef haline gelmiştir.

Son yıllarda yapılan çalışmalar, probiyotikler ve prebiyotikler gibi bağırsak mikrobiyotasını düzenleyici ajanların, kardiyovasküler hastalıkların önlenmesi ve tedavisinde etkili olabileceğini göstermektedir. Akdeniz diyeti gibi sağlıklı beslenme alışkanlıkları, mikrobiyota dengesini koruyarak inflamasyonu azaltarak vasküler sağlığı iyileştirebilir. Ayrıca, fekal mikrobiyota transplantasyonu gibi yenilikçi terapötik yaklaşımlar, metabolik sendrom ve ilişkili kardiyovasküler hastalıkların yönetiminde umut vadedici sonuçlar ortaya koymaktadır. Ancak, bu tedavi yaklaşımlarının uzun vadeli etkileri ve güvenilirliği hakkında daha fazla çalışmaya ihtiyaç duyulmaktadır.

Gelecekte, bağırsak mikrobiyotasının kardiyovasküler hastalıklar üzerindeki etkilerini daha iyi anlamak için kapsamlı klinik araştırmalara ihtiyaç vardır. Özellikle kişiye özel mikrobiyota bazlı tedavilerin geliştirilmesi, kardiyovasküler sağlığın korunması ve hastalık risklerinin azaltılması açısından büyük önem taşımaktadır. Bu bağlamda, multidisipliner araştırmaların artırılması ve bireyselleştirilmiş tıp uygulamalarının desteklenmesi, gelecekte daha etkili ve güvenilir tedavi seçeneklerinin ortaya çıkmasını sağlayacaktır.

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BÖLÜM 3

BIOMARKERS IN HEART FAILURE: DIAGNOSTIC, PROGNOSTIC, AND THERAPEUTIC IMPLICATIONS

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Introduction

Heart failure (HF) is a complex clinical syndrome characterized by the heart's inability to pump blood adequately, leading to symptoms such as dyspnea, fatigue, and fluid retention. It poses a major global health challenge, with an estimated prevalence exceeding 55 million people worldwide and rising due to an aging population and improved survival from acute cardiac events (Roger, 2021; Yan et al., 2023). HF affects approximately 1–2% of adults in developed countries and carries high morbidity and mortality, with 5-year survival rates comparable to many cancers (Roger, 2021). The economic burden is substantial – in the United States, HF-related costs were about $30.7 billion in 2012 and are projected to double by 2030 (Heidenreich et al., 2013; Bhatnagar et al., 2022). These costs stem from frequent hospitalizations, long-term pharmacotherapy, and advanced interventions, underscoring the

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need for strategies to improve early diagnosis, risk stratification, and management of HF (Bhatnagar et al., 2022).

Biomarkers have emerged as valuable tools in addressing these challenges. A biomarker is objectively measured as an indicator of normal biological processes, pathogenic processes, or responses to a therapeutic intervention. In HF, biomarkers can reflect various pathophysiological pathways – myocardial stretch, myocyte injury, neurohormonal activation, inflammation, oxidative stress, fibrosis, renal dysfunction, among others – providing insight into disease presence and severity (Javed & Vittorio, 2024; Ibrahim & Januzzi, 2018). Clinically, biomarkers play pivotal roles in diagnosing HF (especially acute decompensated HF where clinical presentation can mimic other conditions), stratifying prognosis, and in some cases guiding therapy (Javed & Vittorio, 2024; Yancy et al., 2017). For example, natriuretic peptides are now firmly established in guidelines to aid in diagnosing HF and estimating risk (Yancy et al., 2017; McDonagh et al., 2021). Biomarker-guided management has been investigated as a strategy to personalize therapy intensity based on risk profiles, although results have been mixed (Felker et al., 2017). As HF is a heterogeneous syndrome with varying etiologies (ischemic, hypertensive, valvular, etc.) and phenotypes (HF with reduced vs. preserved ejection fraction), a multimarker approach is increasingly considered, combining biomarkers to capture different aspects of the disease process for more precise risk assessment (Kakkar & Lee, 2011; Biasucci et al., 2021). Furthermore, emerging biomarkers from genomics, proteomics, and metabolomics ("omics" technologies) hold promise in improving our understanding of HF and moving toward a precision medicine approach (Licordari et al., 2024; Kennedy & Gaggin, 2023).

This chapter provides a comprehensive overview of biomarkers in both chronic HF and acute decompensated HF. We discuss major classes of biomarkers including natriuretic peptides,

troponins, inflammatory cytokines, oxidative stress markers, fibrosis markers, renal function markers, and novel omics-based biomarkers and evaluate their diagnostic utility, prognostic significance, and therapeutic implications. We also highlight limitations of current biomarkers and future directions, including emerging markers and the potential for integrated multi-biomarker strategies.

Classification of Biomarkers

Over the past few decades, a wide array of biomarkers has been identified in HF, reflecting the multifaceted pathophysiology of the syndrome. Biomarkers can be classified according to the primary pathophysiological mechanism they represent (Javed & Vittorio, 2024; Sarhene et al., 2019). **Table 1** outlines major categories of HF biomarkers and representative examples of each:

Table 1. Mechanistic classification of key heart failure biomarkers (Javed & Vittorio, 2024; Ibrahim & Januzzi, 2018).

Mechanistic Category	Examples of Biomarkers
Myocardial stretch	B-type natriuretic peptide (BNP); N-terminal pro–B-type natriuretic peptide (NT-proBNP); mid-regional pro-atrial natriuretic peptide (MR-proANP)
Myocyte injury	Cardiac troponin I and T (especially high-sensitivity assays); creatine kinase-MB (CK-MB); heart-type fatty acid binding protein (H-FABP); myosin light chain-1
Neurohormonal activation	Norepinephrine; renin–angiotensin–aldosterone system markers (plasma renin activity, angiotensin II, aldosterone); arginine vasopressin and copeptin (its stable peptide); adrenomedullin and MR-proADM; endothelin-1; chromogranins (A/B)
Inflammation	C-reactive protein (CRP); interleukins (e.g., IL-6, IL-1β, IL-18); tumor necrosis factor-α (TNF-α) and soluble TNF receptors; chemokines and other cytokines (e.g., ST2 is also inducible by IL-33)
Oxidative stress	Myeloperoxidase (MPO); oxidative metabolites (e.g., oxidized LDL, isoprostanes, malondialdehyde); uric acid (as an indirect marker)
Myocardial fibrosis and remodeling	Soluble ST2 (sST2); galectin-3; matrix metalloproteinases (MMP-2, -3, -9) and tissue inhibitors of metalloproteinases (TIMPs); collagen turnover fragments (e.g., procollagen peptides); circulating microRNAs related to fibrosis/remodeling
Apoptosis and cell stress	Growth differentiation factor-15 (GDF-15); insulin-like growth factor-binding protein 7 (IGFBP7)
Renal function and injury	Serum creatinine, blood urea nitrogen (BUN), estimated glomerular filtration rate (eGFR); cystatin C; neutrophil gelatinase-associated lipocalin (NGAL); kidney injury molecule-1 (KIM-1) (renal markers reflecting cardiorenal interplay)

Note: Many biomarkers have overlapping significance (for example, GDF-15 is often elevated in HF as a general stress marker), and some fit multiple categories. Markers of end-organ function/dysfunction (such as hepatic enzymes or hematologic indices like hemoglobin and red cell distribution width) are also important in HF but are not primary cardiac biomarkers per se. This

classification emphasizes cardiac and systemic biomarkers directly reflecting HF pathophysiology.

Given this broad spectrum, clinicians and researchers often distinguish established biomarkers – those widely validated and used in practice (such as natriuretic peptides and troponins) – from emerging biomarkers that are under investigation (Ibrahim & Januzzi, 2018; Berezin & Berezin, 2023). In general, an ideal HF biomarker would be specific to HF pathophysiology, sensitive for detection, provide prognostic information incremental to clinical assessment, and be actionable (guiding therapy) while also being cost-effective and readily measurable (Yancy et al., 2017; Kakkar & Lee, 2011). In reality, no single biomarker fulfills all these criteria, so a combination of markers is often considered to obtain a more complete picture of a patient's status (Kakkar & Lee, 2011). In the sections below, we detail the major biomarker types and their clinical applications.

Diagnostic Utility

One of the most important uses of biomarkers in HF is to aid in diagnosis, especially in acute settings. Diagnosing HF can be challenging because symptoms (e.g., dyspnea, edema) and signs (e.g., rales, elevated jugular venous pressure) are not specific to HF and can be seen in other conditions like pulmonary disease, obesity, or renal failure (Fonseca, 2006). Biomarkers can help differentiate cardiac vs. non-cardiac causes of these presentations.

Natriuretic Peptides (BNP and NT-proBNP): The natriuretic peptides are the cornerstone biomarkers for HF diagnosis. BNP and NT-proBNP are released by ventricular myocardium in response to elevated wall stress (ventricular stretch or volume/pressure overload), and they promote vasodilation and natriuresis as counter-regulatory hormones (Maisel & Daniels, 2012). In the context of acute dyspnea, a high BNP or NT-proBNP

level strongly suggests HF as the cause of symptoms, whereas normal levels make HF unlikely (McCullough et al., 2002; Maisel et al., 2002). In the pivotal Breathing Not Properly study, BNP testing improved diagnostic accuracy for acute HF over clinical assessment alone (Maisel et al., 2002). Similarly, the BNP Multinational Study and others demonstrated that adding BNP measurement to clinical judgment significantly increased sensitivity and specificity for diagnosing HF in the emergency department (McCullough et al., 2002). NT-proBNP, the N-terminal cleavage fragment of proBNP, has a longer half-life (≈70 minutes) and is cleared renally, but it likewise rises with hemodynamic cardiac stress and has comparable diagnostic utility (Januzzi et al., 2006). An international pooled analysis of 1,256 patients found that NT-proBNP levels had high sensitivity (≈90%) and specificity (≈84–90% depending on age stratification) for diagnosing acute HF when using age-adjusted cut-offs (Januzzi et al., 2006). Guideline-recommended rule-out thresholds (for example, NT-proBNP <300 pg/mL in acute onset dyspnea, or BNP <100 pg/mL) are used in emergency settings to effectively exclude HF, given their high negative predictive value (Yancy et al., 2017; McDonagh et al., 2021). Conversely, very elevated levels (e.g., NT-proBNP in the thousands pg/mL range) strongly support HF in a patient with compatible symptoms. Notably, *chronic* HF patients have higher baseline NP levels than healthy individuals, so higher thresholds are applied in chronic ambulatory settings (McDonagh et al., 2021). Age, sex, and body habitus also influence NP concentrations: older patients and women tend to have higher NP levels, whereas obese patients have lower circulating NP levels (Bayes-Genis et al., 2007; Ibrahim & Januzzi, 2018). Clinicians must interpret NP values in context – for instance, an obese patient with HF might have a BNP that is only modestly elevated, while a patient with renal impairment can have chronically high NT-proBNP even without acute decompensation (Anwaruddin et al., 2006; Bayes-Genis et al., 2007). Despite these nuances,

natriuretic peptides remain indispensable diagnostic biomarkers, and their use has been shown to be cost-effective by reducing misdiagnosis and hospital admission times for dyspnea patients (Mueller et al., 2004; Moe et al., 2007). An enlarged role for NP measurement is also recognized in HF with preserved ejection fraction (HFpEF), although sensitivities are lower in HFpEF than in HF with reduced EF due to lower wall stress for a given level of symptoms (Yancy et al., 2017).

Beyond BNP and NT-proBNP, other natriuretic peptides have diagnostic roles. Atrial natriuretic peptide (ANP), released from atrial myocardium under stretch, and its stable pro-peptide (MR-proANP) have shown utility in acute HF diagnosis similar to BNP (Maisel et al., 2010). The BACH trial (Biomarkers in Acute Heart Failure) demonstrated that MR-proANP can help identify acute HF, and in some analyses it performed as well as BNP for diagnostic discrimination (Maisel et al., 2010). ANP/proANP levels also rise in HF and correlate with disease severity; however, ANP is less frequently measured in practice compared to BNP/NT-proBNP. The presence of multiple natriuretic peptides underscores the robust response of the heart to hemodynamic stress and provides multiple opportunities for diagnostic testing (Maisel et al., 2010). Clinicians typically rely on BNP or NT-proBNP as they are widely available and well-validated.

Cardiac Troponins: Cardiac troponin I and T are the definitive biomarkers for myocardial injury (especially myocardial infarction), but they also have diagnostic and prognostic implications in HF. Troponins are often elevated in acute decompensated HF even in the absence of an acute coronary syndrome, due to supply-demand mismatch, subendocardial ischemia, or ongoing myocyte necrosis from the failing heart (Pascual-Figal et al., 2012; Tang et al., 2013). Therefore, troponin is measured in all acute HF admissions primarily to screen for

concomitant acute ischemia as a precipitant of decompensation (guidelines recommend checking troponin in acute HF presentations to evaluate for possible acute coronary syndrome) (Yancy et al., 2017). Modestly elevated troponin levels in acute HF without acute myocardial infarction are common and indicate more severe cardiac stress and injury. While troponin is not specific for HF (an elevated troponin does not diagnose HF – it could be due to myocardial infarction or other injuries), the detection of troponin in a patient known to have HF does point to a higher risk state and often worse acute hemodynamics (Pascual-Figal et al., 2012). For example, in the ADHERE registry of acute HF hospitalizations, 6.2% of patients had a positive conventional troponin, and this was associated with higher in-hospital mortality (odds ratio ~2.5) (Tang et al., 2013). With high-sensitivity assays, troponins are detectable in a majority of chronic HF patients as well, reflecting low-level ongoing myocardial injury. Thus, troponins have limited utility in diagnosing chronic HF (since their presence is not specific), but their measurement on admission for acute HF is useful to rule out myocardial infarction and to risk-stratify (Pascual-Figal et al., 2012). In summary, an elevated troponin in acute or chronic HF should prompt careful evaluation for ischemic triggers but, if alternative causes are excluded, generally signifies a more advanced or severe HF state. Troponin levels do not distinguish HF from non-HF causes of dyspnea, so they cannot replace natriuretic peptides in diagnosing HF; rather, they complement NPs by providing prognostic information and uncovering ischemic etiology (Gaggin et al., 2013b).

Other Biomarkers for Diagnosis: Inflammatory markers and others are not primary diagnostic tests for HF, but they can provide supportive information or help in differential diagnosis. For instance, a significantly elevated high-sensitivity C-reactive protein (CRP) or interleukin-6 (IL-6) level in a dyspneic patient might suggest a

systemic inflammatory state or infection exacerbating HF vs. an isolated cardiac cause, but these are non-specific findings (Sarhene et al., 2019). Novel biomarkers like soluble ST2 and galectin-3 are more for prognosis and are not used to diagnose HF acutely. Markers of renal function (creatinine, cystatin C) are important in evaluating a patient with suspected HF because renal impairment can cause fluid retention and also elevate natriuretic peptides (via reduced clearance), but again, they are not specific to diagnosing HF (Anwaruddin et al., 2006). Ultimately, the current diagnostic strategy for HF relies on clinical evaluation plus natriuretic peptide testing and imaging (echocardiography) for confirmation of cardiac dysfunction. Biomarkers augment the accuracy of the initial clinical assessment. In primary care, NP testing is particularly useful to decide who needs further cardiac imaging (Fonseca, 2006). As an example, low NT-proBNP can effectively rule out HF in a patient with chronic dyspnea, avoiding unnecessary referral, whereas a high value prompts expedited cardiology evaluation (Yancy et al., 2017). Studies have shown that using NP cutoffs in outpatient settings improves the timing of HF diagnosis and reduces missed HF cases (McDonagh et al., 2017 update; Fonseca, 2006).

In acute decompensated HF (ADHF), combining biomarkers may further assist with diagnosis in challenging cases. For example, the BACH trial showed that adding MR-proADM and copeptin to BNP improved diagnostic accuracy in certain subgroups, such as patients with concurrent COPD or obesity, where BNP alone might be ambiguous (Maisel et al., 2010; Shah et al., 2012). However, routine use of multiple biomarkers for acute diagnosis has not become standard, due to cost and practicality. BNP/NT-proBNP remains the primary biochemical test for HF diagnosis.

In summary, the natriuretic peptides are indispensable diagnostic biomarkers in HF, providing high sensitivity for ruling out the disease and good positive predictive value when markedly

elevated (Maisel et al., 2002; Januzzi et al., 2006). Troponins are measured alongside to detect myocardial infarction and gauge severity. Other biomarkers are generally not used in isolation for diagnosis but can contribute to the overall clinical assessment. The integration of biomarker data with clinical and imaging findings results in the most accurate diagnosis of HF (Yancy et al., 2017). As new markers emerge, there is potential to refine diagnostic algorithms, for example using machine learning on panels of markers to distinguish HF from other causes of dyspnea but such approaches remain investigative. Current guidelines strongly endorse NP testing in both acute and ambulatory care when HF is suspected (Yancy et al., 2017; Chow et al., 2017).

Prognostic Significance

Biomarkers provide powerful prognostic information in HF, often reflecting disease severity and risk of adverse outcomes such as hospitalization and mortality. Risk stratification is crucial in HF management to identify patients who may benefit from intensified therapy or advanced interventions. Many biomarkers that are elevated in HF have been shown to correlate with worse outcomes, independent of traditional clinical predictors.

Natriuretic Peptides: Beyond diagnosis, elevated BNP and NT-proBNP are consistently associated with poorer prognosis in both acute and chronic HF. Higher NP levels generally indicate higher ventricular filling pressures and wall stress, which correspond to more advanced HF. For acute decompensated HF, admission BNP/NT-proBNP levels stratify in-hospital and short-term outcomes: for example, the ADHERE registry found that patients presenting with BNP in the highest quartile (BNP ≥ ~1,700 pg/mL) had more than double the in-hospital mortality of those in the lowest quartile (Fonarow et al., 2007). Similarly, an analysis showed NT-proBNP >986 pg/mL on admission was associated with nearly a

three-fold increase in 1-year mortality compared to lower levels (Berger et al., 2024). In both HF with reduced EF (HFrEF) and HFpEF, higher NPs portend higher risk, although absolute NP values tend to be lower in HFpEF for a given level of risk (Berger et al., 2024). Prognostic use of NPs extends to chronic HF as well: in the Val-HeFT trial, patients with rising NT-proBNP over a 4-month period had significantly higher subsequent mortality than those whose NT-proBNP remained low or decreased (Masson et al., 2008). In fact, serial measurement can improve risk prediction – the trajectory of NP levels (whether they are increasing or decreasing with therapy) carries prognostic weight (Masson et al., 2008). A patient whose NT-proBNP remains very high at discharge from a hospitalization or rises on follow-up is at high risk for rehospitalization or death within months, whereas a patient whose levels drop significantly with treatment generally has a better short-term outlook (Wettersten, 2021). Because of this, NPs are often incorporated into multifactorial risk scores for HF. Some guidelines suggest that persistently elevated natriuretic peptide levels should prompt consideration of advanced therapies or closer monitoring (Yancy et al., 2017). However, it's worth noting that extremely elevated NP levels can sometimes reflect chronic stable elevation in certain individuals (e.g., with chronic renal disease), so trends and clinical context matter (Anwaruddin et al., 2006). Nonetheless, meta-analyses confirm that BNP and NT-proBNP are strong, independent predictors of mortality and HF hospitalization across the spectrum of HF patients (Sarhene et al., 2019).

Cardiac Troponins: Detectable or elevated troponin levels in HF patients are consistently associated with adverse outcomes. In chronic HFrEF, high-sensitivity troponin T (hsTnT) is measurable in a large majority of patients, and levels above the 99th percentile (even minor elevations) correlate with worse long-term prognosis (Motiwala et al., 2015). For instance, one study in ambulatory

HFrEF found that hsTnT >0.012 ng/mL was associated with a two-fold higher risk of death or HF hospitalization over ~2 years (Motiwala et al., 2015). In acute HF, troponin elevation on admission identifies patients at greater risk of in-hospital and early post-discharge mortality (Pascual-Figal et al., 2012). Moreover, changes in troponin over time may have prognostic value: an increase in hsTn over a 3-month period in chronic HF patients was linked to higher mortality compared to patients whose hsTn remained stable (Gaggin et al., 2013b). Troponin thus provides prognostic insight complementary to natriuretic peptides – reflecting ongoing myocardial injury/remodeling rather than hemodynamic stress. Importantly, troponin and NP often predict outcomes independently of each other (Pascual-Figal et al., 2012). In the RELAX-AHF trial data, hsTnT added prognostic information on top of NT-proBNP for 180-day outcomes in acute HF (Pang et al., 2016). Persistent troponin elevation in chronic HF can identify a subgroup with progressive adverse remodeling who may need more aggressive therapy or advanced HF referral. However, as of now, troponin is primarily a risk marker; no specific HF therapy is directed at lowering troponin levels (Gaggin et al., 2013b). Still, its presence signals higher risk for arrhythmias, pump failure, and mortality. For example, in one study of stable HF patients, those with rising hsTnI had a significantly shorter time to required transplantation or death (Motiwala et al., 2015). Overall, troponin is a potent prognostic biomarker in HF – the adage is that "any troponin elevation in HF is bad."

Soluble ST2: ST2 is the receptor for interleukin-33 and is released in its soluble form by cardiomyocytes and fibroblasts under mechanical strain and inflammatory stimulation. Soluble ST2 has emerged as one of the most robust prognostic biomarkers in HF. Multiple studies have shown that elevated sST2 levels correlate with higher mortality and HF hospitalization rates, independent of NPs

and clinical variables (Aimo et al., 2017). A meta-analysis of chronic HF patients found that those in the highest ST2 quartile had about 2.5-fold higher risk of mortality compared to those in the lowest quartile (Aimo et al., 2017). ST2 is particularly interesting because it appears less affected by typical confounders like age, obesity, or renal function, making it a relatively reliable marker across diverse populations (Januzzi et al., 2007). In the PRIDE study of acute dyspneic patients, ST2 levels >0.20 ng/mL were strongly predictive of 1-year mortality, and ST2 added prognostic value on top of NT-proBNP (Januzzi et al., 2007). Unlike natriuretic peptides, ST2 is thought to reflect fibrosis and remodeling activity in the myocardium; higher ST2 indicates more active adverse remodeling, which portends worse outcomes. In chronic HF, serial monitoring of ST2 has shown that patients with consistently high ST2 or a rise in ST2 have substantially higher risk of events than those whose ST2 remains low (Gaggin et al., 2013a). One analysis found that patients with persistently elevated ST2 over 10 months were more than 3.5 times as likely to experience cardiovascular death or HF hospitalization compared to those with low ST2 (Gaggin et al., 2013a). These findings have led to ST2 being incorporated into risk stratification and it is now FDA-cleared for prognostication in HF. For example, an ST2 level above ~35 ng/mL is generally considered high-risk. Some HF specialists will measure ST2 periodically in advanced HF patients to help determine when to escalate therapy or refer for transplant/ventricular assist device. Notably, ST2 levels tend to decrease in patients responding well to HF therapies (such as beta-blockers or mineralocorticoid receptor antagonists), although certain treatments (e.g., MRAs) can also biologically lower ST2, potentially confounding interpretation (Gaggin et al., 2013a). Overall, the evidence base for ST2's prognostic power is strong, and its addition to standard risk models significantly improves prediction of mortality (Aimo et al., 2017). This has been recognized in

guidelines – the 2017 ACC/AHA update acknowledged ST2 as an additive prognostic marker to NPs (Yancy et al., 2017).

Galectin-3: Galectin-3 is a beta-galactoside-binding lectin secreted by activated macrophages, implicated in fibrosis and cardiac remodeling. It was one of the first fibrosis biomarkers to be FDA-approved for HF risk stratification. Studies show that elevated galectin-3 levels are associated with worse outcomes, especially in acute HF or advanced HF. For example, one study of acute HF patients found those in the top quartile of galectin-3 had dramatically higher 60-day mortality (odds ratio ~10 for death) and higher rates of early readmission (Javed & Vittorio, 2024; van Kimmenade et al., 2006). In chronic HF, galectin-3 also correlates with mortality and hospitalization risk, but its prognostic value has been somewhat variable between studies (Lok et al., 2013; Javed & Vittorio, 2024). Some analyses found galectin-3 to be an independent predictor of death or HF hospitalization in chronic HF (Lok et al., 2013), while others showed that when adjusted for NT-proBNP and renal function, galectin-3's prognostic significance attenuated. A meta-analysis concluded that elevated galectin-3 is associated with higher mortality in both acute and chronic HF, but the effect size is moderate (Hu et al., 2018). Notably, galectin-3 tends to change slowly over time and may not drop with standard HF therapy, suggesting it reflects a relatively fixed fibrosis burden (de Boer et al., 2013). Serial galectin-3 measurements in the HF-ACTION study did not show significant associations with changes in outcomes, in contrast to ST2 (Gaggin et al., 2013a). Therefore, while a high galectin-3 (e.g., >17–25 ng/mL depending on assay) indicates higher risk (roughly 1.5 to 2-fold higher mortality risk for top vs bottom quartile), its role in monitoring or guiding therapy is less clear. Galectin-3 is considered a complementary risk marker – it may identify patients with a profibrotic phenotype who have worse prognosis, potentially guiding enrollment in trials of antifibrotic therapies in the future. The

cost of galectin-3 testing is relatively high and its incremental predictive power on top of NPs and clinical variables is modest, which has limited its widespread adoption (Javed & Vittorio, 2024). Nonetheless, it remains an interesting biomarker linking macrophage-driven fibrosis to HF outcomes and is part of the "multimarker" panels in some risk models.

Inflammatory Markers (CRP, IL-6, etc.): Chronic inflammation contributes to HF progression, especially in HFpEF and in patients with comorbidities. Higher levels of inflammatory biomarkers such as high-sensitivity CRP and interleukin-6 are associated with worse prognosis in HF. In the BIOSTAT-CHF study, IL-6 was found to be an independent predictor of mortality particularly in HFpEF patients (Berger et al., 2024). HFpEF patients with elevated IL-6 had significantly higher cardiovascular mortality, whereas in HFrEF IL-6 had a weaker association (Berger et al., 2024). This may reflect the prominent role of systemic inflammation in the pathophysiology of HFpEF (e.g., due to metabolic syndrome, obesity, etc.). CRP, a general marker of inflammation, correlates with NYHA class and outcomes as well – HF patients with CRP in the highest tertile have higher mortality than those with low CRP (Sarhene et al., 2019). However, because inflammatory markers are so non-specific, it is challenging to use a specific threshold in practice to change management. They often mirror the severity of HF or comorbid conditions (e.g., infection, obesity) rather than purely cardiac status. Nonetheless, they provide insight into risk: an HF patient with elevated IL-6 or CRP is likely sicker and at higher risk of adverse events (Sarhene et al., 2019; Berezin & Berezin, 2023). Tumor necrosis factor-alpha (TNF-α) and its receptors were among the first inflammatory cytokines studied in HF; elevated levels of TNF-α and soluble TNF receptors are linked with cardiac cachexia and poor outcomes. Indeed, high circulating TNF was associated with worse functional status and mortality, though clinical

trials targeting TNF (e.g., etanercept) did not improve outcomes, possibly because by the time TNF is elevated, downstream damage is done. Other inflammatory mediators like pentraxin-3, ST2 (reflecting an interleukin family pathway), and osteoprotegerin have all been shown in studies to predict outcomes to varying degrees (Sarhene et al., 2019). An emerging concept is that a subset of HF patients have a high "inflammatory biomarker profile" which might benefit from therapies targeting inflammation; ongoing trials (e.g., testing IL-1 or IL-6 antagonists in HF) are exploring this. For now, measuring IL-6 or CRP is not routine in HF care, but these markers clearly indicate prognosis in research settings (Berger et al., 2024).

Oxidative Stress Markers: Oxidative stress plays a role in the pathogenesis of HF by causing cellular damage and endothelial dysfunction. Markers of oxidative stress have been studied for prognosis. One example is **myeloperoxidase (MPO)**, an enzyme released by activated neutrophils that produces reactive oxidant species. Elevated MPO levels have been associated with incident HF development and with worse outcomes in established HF. In a prospective study of older adults without HF at baseline, higher plasma MPO predicted an increased risk of developing HF over time (Tang et al., 2009). In patients hospitalized with acute HF, those with the highest MPO levels had significantly higher 1-year mortality compared to those with lower levels (Tang et al., 2009). This suggests MPO may identify patients with an ongoing inflammatory-oxidative process contributing to myocardial and vascular dysfunction. Other oxidative markers include malondialdehyde and isoprostanes (by-products of lipid peroxidation), which have been found at higher levels in HF patients and relate to disease severity (Sarhene et al., 2019). Uric acid is sometimes considered a rough index of oxidative stress and poor man's marker; high uric acid is common in HF and correlates with worse NYHA class and outcomes (it was a risk factor in the ESC HF Long-Term Registry), though

confounded by renal function and diuretic use. Overall, while oxidative stress markers are prognostic in research studies, they are not measured clinically for risk stratification due to assay complexity and unclear incremental benefit. They do reinforce that patients with an activated neutrophil or oxidative profile (often those with ischemic HF or diabetes) fare worse. Future therapies aiming to reduce oxidative stress (e.g., specific antioxidants or xanthine oxidase inhibitors) could potentially use these biomarkers to identify responsive patients.

Fibrosis and Remodeling Markers: Biomarkers reflecting extracellular matrix remodeling and fibrosis are strongly prognostic, as they directly relate to adverse cardiac remodeling. We discussed ST2 and galectin-3 above, which are key fibrosis-related markers. Beyond those, circulating levels of collagen synthesis or degradation products have been linked to outcomes. For example, elevated serum procollagen type III N-terminal peptide (PIIINP), a marker of collagen turnover, was associated with higher mortality in HFrEF and was shown to decrease with effective therapy like spironolactone (Zannad et al., 2000). Matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) regulate extracellular matrix breakdown; imbalances in these can lead to pathological fibrosis and dilation. In one study, high MMP-2 levels predicted higher mortality in HF (George et al., 2005), and another found elevated MMP-9 associated with worse outcomes (Ballo et al., 2010). These findings tie into the observation that patients with more myocardial fibrosis (as seen on cardiac imaging with late gadolinium enhancement or high extracellular volume on cardiac MRI) have poorer prognoses. Soluble biomarkers serve as indirect measures of that fibrotic burden. IGFBP7, noted earlier, is another novel marker that may relate to fibrotic or cell senescence pathways; in HFpEF, high IGFBP7 was associated with worse diastolic function and independently predicted mortality (Gandhi et al., 2017). GDF-15,

which can be considered an oxidative stress and apoptosis marker, also correlates with fibrosis and remodeling extent; higher GDF-15 levels in HF patients predict greater risk of death or HF admission (Kempf et al., 2007). A unique aspect of fibrosis markers is that they might identify patients who could benefit from therapies targeting fibrosis (for example, trials of anti-fibrotic drugs or mineralocorticoid receptor antagonists might stratify by baseline fibrosis marker levels). At present, ST2 and galectin-3 are the main fibrosis biomarkers in clinical use, but research continues on collagen fragments and other remodeling indicators.

Renal Biomarkers (Cardiorenal interplay): Worsening renal function in HF is a well-known risk factor for poor outcomes. Biomarkers that capture renal impairment or injury have prognostic value in HF. Traditional measures like creatinine and eGFR are already part of risk models – lower eGFR is associated with higher mortality in HF. **Cystatin C**, an alternative measure of GFR that is less influenced by muscle mass, has been found to be an even stronger predictor of mortality than creatinine in HF patients (Damman et al., 2007). In a meta-analysis, patients with serum cystatin C in the highest tertile had about 1.6 times the risk of death or HF hospitalization compared to those in the lowest tertile (Kumar et al., 2024). Cystatin C may reclassify risk especially in those who appear to have “normal” creatinine but actually have reduced GFR. **Neutrophil gelatinase-associated lipocalin (NGAL)**, a marker of acute kidney injury, is elevated in HF (even chronic HF) due to subclinical renal tubular injury from congestion or poor perfusion. Elevated plasma NGAL predicts higher risk of death in both acute and chronic HF patients, including those without overt chronic kidney disease (Chan et al., 2012). One study reported that HF patients with NGAL in the highest quartile had nearly a three-fold increased hazard of mortality relative to those with the lowest levels (Kumar et al., 2024). NGAL is also predictive of acute kidney injury

during hospitalization for HF and of the cardiorenal syndrome (Kumar et al., 2024). Thus, renal biomarkers add prognostic information by capturing the kidney's status, which is intimately linked to HF outcomes. The concept of a "cardiorenal risk marker" panel has been proposed, combining NPs with cystatin C or NGAL to better stratify risk than NPs alone (Kumar et al., 2024). While not yet routine, some clinicians do measure cystatin C to refine risk assessment. It is important to note these markers often correlate with each other – for instance, a patient with high NT-proBNP often has some degree of renal impairment reflected in cystatin C – but each sheds light on a different facet (hemodynamic load vs. renal filtration). *Blood urea nitrogen (BUN)*, though a crude marker, has surprisingly strong prognostic power in acute HF: a high BUN on admission (e.g., >30 mg/dL) is a simple predictor of in-hospital mortality, likely reflecting low cardiac output and renal hypoperfusion. Finally, emerging renal markers like **KIM-1** (kidney injury molecule-1) have shown associations with HF outcomes, particularly with risk of worsening renal function during treatment (Kumar et al., 2024).

Endothelial Dysfunction Markers: Markers such as soluble CD146 (a cell adhesion molecule) and circulating endothelial progenitor cells have been examined, but their clinical utility is not established. One notable peptide is **adrenomedullin**, a vasodilatory hormone. High adrenomedullin levels have been linked to severe HF and poor prognosis, and a stable fragment (MR-proADM) was a strong predictor of 1-year mortality in acute HF in the BACH trial (Maisel et al., 2010). A prospective study showed MR-proADM was one of the best single predictors of mortality among various biomarkers tested (Voors et al., 2019). This reflects that endothelial and vascular dysfunction (with high adrenomedullin as a compensatory response) is a marker of high-risk HF. Another marker, **copeptin**, the C-terminal segment of vasopressin pro-

hormone, indicates arginine vasopressin activation. In acute HF, elevated copeptin predicted higher 90-day mortality, especially in hyponatremic patients, beyond what NP indicated (Maisel et al., 2011). These observations underscore that the more systems are activated (neurohormonal, renal, inflammatory), the worse the prognosis.

In summary, virtually every biomarker elevated in HF has some prognostic implication. Table 2 provides a high-level summary of key biomarkers and their prognostic significance. The integration of multiple biomarkers yields the most robust risk stratification. Indeed, studies have shown that multi-marker models (e.g., combining NP, troponin, ST2, and galectin-3) significantly improve mortality prediction over any single marker (Gaggin et al., 2013b; Ibrahim & Januzzi, 2018). However, the added complexity and cost of measuring many biomarkers has to be balanced against incremental benefit. Clinically, natriuretic peptides remain the workhorse for prognostication (routine in all HF patients), and troponin is often considered. ST2 and galectin-3 are available for use and can help in selected cases (especially for advanced HF risk assessment). Others are primarily research tools at this time. Prognostic stratification is not merely an academic exercise; it can inform intensity of follow-up, consideration of advanced therapies, and discussions with patients about expected outcomes. Biomarkers have transformed our ability to quantify risk in HF, moving beyond clinical gestalt to objective measures of disease biology (Ibrahim & Januzzi, 2018).

Table 2. *Selected Heart Failure Biomarkers and their Prognostic Implications.*

Biomarker	Key Prognostic Significance and Clinical Implications	Limitations/Notes
BNP / NT-proBNP	Higher levels correlate with worse NYHA class and higher risk of mortality and rehospitalization in both acute and chronic HF. A drop in levels with therapy is favorable, while rising or persistently high levels signal high risk (Fonarow et al., 2007; Masson et al., 2008). Often used to monitor disease trajectory; integrated into risk scores.	Levels affected by age, obesity (lower), renal dysfunction (higher). Need HF-specific cutoffs; not all "elevations" equal in different patients (Yancy et al., 2017).
Cardiac Troponin (hs-cTn)	Any detectable troponin in chronic HF or acute HF (absent an MI) indicates ongoing myocardial injury and portends higher mortality and hospitalization risk (Pascual-Figal et al., 2012; Motiwala et al., 2015). Patients with rising troponin over time have worse prognosis. Useful to identify high-risk patients who may need aggressive therapy or evaluation for ischemia.	Very nonspecific for HF (elevated in many conditions); not a therapy target. In acute HF, often elevated due to demand ischemia – signals severity but cannot distinguish acute MI without ECG/imaging.
Soluble ST2	Strong independent predictor of mortality and HF hospitalization. High sST2 (>35 ng/mL) is associated with markedly elevated risk; those with persistently high or rising ST2 have poor outcomes (Aimo et al., 2017; Januzzi et al., 2007). Adds prognostic value even when NP and clinical risk factors are known. May identify patients with ongoing	Less affected by confounders, which is a strength. Not yet universally measured due to cost; unclear optimal monitoring frequency. Not specific to HF (elevated in other inflammatory states, though threshold of 35 ng/mL is quite specific for high risk in HF).

	fibrosis/remodeling – potential to guide timing of advanced therapies.	
Galectin-3	Elevated galectin-3 (>17–25 ng/mL, assay-dependent) predicts higher risk of short-term mortality and readmission, especially in acute HF (van Kimmenade et al., 2006). In chronic HF, higher galectin-3 is associated with long-term mortality and more rapid progression in some studies (Lok et al., 2013). Reflects fibrotic and inflammatory activity.	Some variability in prognostic results; often loses significance after adjusting for renal function or NP. Changes slowly and does not appear to respond to standard HF therapy, limiting its use as a serial marker (de Boer et al., 2013). Expensive test.
CRP and IL-6 (Inflammation)	High CRP and IL-6 levels are associated with more advanced HF and increased mortality (Sarhene et al., 2019; Berger et al., 2024). IL-6 is particularly predictive in HFpEF (elevated IL-6 identifies HFpEF patients at higher risk of death) (Berger et al., 2024). These markers highlight patients in whom systemic inflammation is contributing to HF, who may have rapid progression.	Very nonspecific; affected by infections, obesity, etc. Not routinely measured for prognosis due to lack of targeted therapy yet. But could become important if anti-inflammatory treatments prove beneficial in HF.
Myeloperoxidase (Oxidative stress)	High MPO levels in HF patients predict increased risk of HF hospitalization and mortality (Tang et al., 2009). MPO may identify patients with active oxidative stress and inflammation who tend to have ischemic or advanced HF. Elevated MPO in apparently healthy individuals is a risk factor	Research use currently. Lacks a well-defined threshold for clinical use; not measured in practice due to availability of broader inflammatory panels.

	for developing HF over years (Tang et al., 2009).	
GDF-15	An elevated GDF-15 indicates worse prognosis in HF. Higher levels are associated with greater severity (higher NYHA, more cachexia) and independently predict mortality (Kempf et al., 2007). GDF-15 captures aspects of oxidative stress, apoptosis, and inflammation. Prognostic in both HFrEF and HFpEF.	Very high levels can be seen in cancer or renal disease, so not specific. The assay is somewhat specialized. Primarily a research prognostic marker at present.
Cystatin C	Higher cystatin C (worse kidney function) strongly predicts mortality and HF hospitalization. Adds prognostic information beyond creatinine; a better gauge of true GFR in HF patients with low muscle mass (Kumar et al., 2024). In some studies, outperforms creatinine-based eGFR for risk prediction.	Reflects renal function, which is influenced by many factors. Not cardiac-specific. Often moves in parallel with established clinical measures (NYHA class correlates with worse renal function). Used in risk models but not routinely measured clinically if creatinine is available.
NGAL	High plasma NGAL predicts higher mortality in chronic HF, even after accounting for GFR (Chan et al., 2012). In acute HF, high NGAL (plasma or urine) predicts occurrence of acute kidney injury and is linked to short-term adverse outcomes (Damman et al., 2014). Essentially, NGAL signals renal tubular stress/injury from the HF state, and those with such injury fare worse.	Not widely available as a clinical test. Can be elevated in any context of kidney injury (e.g., sepsis, contrast nephropathy). Primarily studied in acute HF settings for AKI prediction.
Adrenomedullin (MR-proADM)	High MR-proADM levels are associated with increased mortality and HF	MR-proADM currently used mostly in research. It may help identify high-

	admissions. One-year mortality risk is significantly higher in patients with top-quartile MR-proADM; it adds prognostic value to NP (Voors et al., 2019; Maisel et al., 2010). Indicates severity of endothelial dysfunction and vasoconstrictive state.	risk acute HF patients who need intensive therapy, but it's not routine due to limited availability.
Others (MMPs, etc.)	Elevated MMP-2, MMP-9 and TIMP levels correlate with worse outcomes as they reflect ongoing remodeling (George et al., 2005; Ballo et al., 2010). Markers like soluble uric acid, anemia indices (low hemoglobin, high RDW), and hepatic enzymes (high AST/ALT from congestion) all carry prognostic information – e.g., anemia and high RDW are well-known predictors of mortality in HF. These are considered in overall assessment.	Many of these are indirect markers and often correlate with known risk factors (e.g., anemia with chronic disease severity). While prognostically useful, they are less specific to HF pathophysiology and often not targeted by therapy (except treating anemia or iron deficiency, which does improve outcomes (McDonagh et al., 2021)).

As **Table 2** illustrates, each biomarker offers a window into a particular aspect of HF pathophysiology, and elevations generally signal higher risk. Clinicians should interpret biomarkers in the context of the whole patient – for example, an elderly patient with chronic HF, CKD, and high CRP might have multiple elevated biomarkers (NP, cystatin C, CRP, troponin) all pointing to high risk, whereas a younger patient with isolated systolic dysfunction post-MI might mainly show elevated NP but normal inflammatory markers. Tailoring monitoring and therapy in response to prognostic biomarkers is an area of active investigation.

Therapeutic Monitoring and Implications

Biomarkers not only inform diagnosis and prognosis, but in some cases can guide therapy or serve as targets to monitor treatment response. The concept of **biomarker-guided therapy** is that adjusting HF treatments to achieve or maintain certain biomarker levels could improve outcomes. This concept has been most extensively studied with natriuretic peptides and, to a lesser extent, with newer markers like ST2.

Natriuretic Peptide–Guided Therapy: Given the strong prognostic value of BNP/NT-proBNP, researchers hypothesized that titrating HF therapy (e.g., diuretics, beta-blockers, ACE inhibitors) to try to lower NP levels might improve outcomes compared to usual care. Several randomized trials and meta-analyses have examined NP-guided therapy, especially in chronic HFrEF. Early single-center trials suggested that NP-guided care might reduce mortality or hospitalization by leading to more aggressive uptitration of medications when NP levels remained high (Troughton et al., 2014). A meta-analysis of small trials indicated a ~20–30% reduction in mortality with NP-guided management (Wettersten, 2021). However, the definitive large trial, **GUIDE-IT** (Felker et al., 2017), did not show a significant difference in outcomes between NT-proBNP-guided therapy versus usual care in high-risk HFrEF patients. In GUIDE-IT, both arms ended up with similar achieved NT-proBNP levels and there was no mortality or hospitalization benefit to the guided strategy (Felker et al., 2017). Several reasons were posited: clinicians in usual care were already optimizing therapy well, some patients' NP levels remain high despite maximal therapy, and co-morbidities can limit up-titration. Subgroup analyses suggested possibly younger patients might benefit from NP-guiding, but overall the strategy did not significantly change practice (Felker et al., 2017). Current guidelines do not universally recommend NP-guided therapy, though they acknowledge it can be considered in

experienced centers for HFrEF (Yancy et al., 2017). In clinical practice, many physicians do monitor NP trends and use them as one factor in decision-making (e.g., if NT-proBNP is rising, they might intensify diuresis or check adherence). The therapeutic implication is that an individual patient whose NP remains very high despite optimal therapy might need advanced therapies (device therapy, transplant evaluation), whereas a patient whose NP normalizes might be stable enough for less frequent visits (Yancy et al., 2017). Additionally, NP levels can help assess response to acute therapy: for example, a significant decline in NT-proBNP during a hospitalization is associated with better post-discharge outcomes (Wettersten, 2021). Many clinicians thus aim for a substantial NP reduction as a sign of successful decongestion. Therapies like renin-angiotensin-aldosterone system (RAAS) inhibitors and beta-blockers typically lead to NP level reductions over months as the heart remodels (Ledwidge et al., 2013), whereas lack of NP improvement might suggest ongoing wall stress and need for further intervention. It should be noted that the introduction of angiotensin receptor–neprilysin inhibitors (ARNIs, e.g., sacubitril-valsartan) complicates NP monitoring: ARNI therapy raises BNP levels (by inhibiting BNP breakdown) even as it lowers cardiac filling pressures, whereas NT-proBNP levels fall on ARNI (because NT-proBNP is not degraded by neprilysin) (ACC, 2015). Therefore, for patients on ARNI, NT-proBNP is the preferred marker to follow, as BNP will be artificially elevated (Chow et al., 2017). This is an example of how therapy can influence biomarker interpretation.

Using Biomarkers to Trigger Therapy Changes: Some biomarkers indicate specific pathways that could be therapeutically targeted. For instance, a high copeptin (surrogate for vasopressin) in a hyponatremic HF patient might prompt consideration of a vasopressin receptor antagonist (tolvaptan) to correct hyponatremia, which was suggested by findings that copeptin predicted benefit

from that therapy (Maisel et al., 2011). Likewise, markedly elevated LDL or Lp(a) in an HF patient would direct aggressive lipid management to reduce ischemic progression (though those are more risk factors than HF biomarkers). Iron status is another important one: HF patients with iron deficiency (low ferritin or transferrin saturation) have worse exercise capacity and outcomes, and trials have shown IV iron therapy improves functional status and may reduce hospitalizations (McDonagh et al., 2021). Thus, while not a "cardiac biomarker" in the traditional sense, checking iron studies and treating iron deficiency is now part of HF therapeutic strategy – an example of biomarker-guided intervention improving outcomes.

Serial Biomarker Monitoring: Regular monitoring of certain biomarkers can inform long-term management. For example, some advanced HF clinics measure NT-proBNP at each visit to track disease trajectory. If NT-proBNP trends upwards over a few months, they might intensify diuretics or add therapies (assuming patient adherence and volume status are suboptimal) (Wettersten, 2021). With the advent of devices capable of measuring surrogates of filling pressure (like implanted pulmonary artery pressure monitors), the role of biomarkers in monitoring may evolve, but currently NP is still a convenient tool. ST2 is a candidate for serial monitoring: as discussed, persistently elevated ST2 identifies patients with ongoing risk. One study suggested managing patients to keep ST2 below 35 ng/mL (through uptitration of evidence-based therapies) was associated with improved ventricular function and fewer events (Gaggin et al., 2013a). There is an intriguing observation that changes in beta-blocker dose correlated with changes in ST2 levels: patients who could tolerate high-dose beta-blockers saw reductions in ST2 and had better outcomes (Gaggin et al., 2013a). This might imply that ST2 could guide therapy intensity – e.g., if ST2 remains high, push doses of beta-blockers or add antifibrotic treatments if available. However, these approaches are not yet standard care; they

are hypothesis-generating findings from cohort studies. Galectin-3 monitoring, on the other hand, has not proven useful; as noted earlier, HF therapies do not seem to lower galectin-3 levels, and serial galectin-3 did not predict outcomes better than a single measurement (de Boer et al., 2013). This suggests that if a biomarker is not modifiable by treatment, it's less useful as a management target (it remains just a risk marker). ST2 appears more dynamic, which is encouraging.

Biomarkers as Targets for Therapy: Another implication is the development of therapies that specifically target pathways identified by biomarker research. For instance, recognizing inflammation's role in HF (through markers like IL-6, CRP) has led to trials of anti-inflammatory therapies (e.g., IL-1 blockers such as anakinra, IL-6 blockers like tocilizumab, or colchicine) in HF to see if outcomes improve by dampening inflammation. Results so far are mixed, but if successful, future HF management could involve checking inflammatory markers and treating accordingly. Similarly, elevated TMAO (a metabolite from gut microbiota) has pointed to the gut-heart axis as a therapeutic target; there is interest in dietary interventions or drugs that reduce TMAO production to see if HF outcomes improve (Hazen et al., 2020). High TMAO levels identify patients at risk for incident HF and worse prognosis (Li et al., 2020), raising the possibility of *treating* the biomarker (e.g., with probiotic therapy or diet) as a means to treat the disease. This is a paradigm shift in some ways: historically, we treat the patient and expect the biomarker to change; here, the biomarker (like TMAO) might itself become a direct target because it's mechanistically involved in HF progression (Li et al., 2020). Another example is neprilysin: elevated neprilysin activity could degrade natriuretic peptides and contribute to HF severity, which was part of the rationale for neprilysin inhibitors (ARNI therapy). There is interest in measuring soluble neprilysin levels as a marker of whether patients would benefit most

from ARNI (though ARNI is broadly beneficial in HFrEF regardless) (Licordari et al., 2024).

Guiding Advanced Therapies: Biomarkers play a role in timing of advanced HF therapies like device implantation or transplant. For instance, persistent very high NP or troponin can support the decision to refer a patient for transplant evaluation, as it indicates high 1-year mortality risk (Yancy et al., 2017). Conversely, a drop in NP with therapy might allow a watch-and-wait approach. Some algorithms for implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy (CRT) placement include NT-proBNP thresholds to refine risk of sudden death vs. pump failure. Additionally, in acute HF, serial NP measurements can indicate whether diuresis is adequate (if NP isn't falling, the patient may still be wet). In cardiogenic shock or acute decompensation, lactate and central venous oxygen saturation are used alongside cardiac biomarkers to guide use of inotropes or mechanical support.

In summary, while biomarker-guided therapy has not yet revolutionized standard HF management (due to trials like GUIDE-IT being neutral), biomarkers are frequently used to *monitor* response to therapy and inform decisions. Therapies proven to improve outcomes in HF (RAAS blockers, beta-blockers, SGLT2 inhibitors, etc.) generally lead to improvement in biomarker profiles over time (NP falls, CRP might fall, etc.), so seeing those changes provides reassurance of efficacy (Wettersten, 2021). If biomarkers worsen, clinicians should reassess adherence, add therapies (e.g., hydralazine-nitrate if NP remains high in a Black patient already on others), or consider advanced options. Biomarkers such as ST2 and troponin are gradually finding their way into practice for refining prognosis, which indirectly affects therapy intensity decisions (for example, a high-risk biomarker profile might prompt closer follow-up and ensuring all possible therapies are on board).

A future therapeutic implication is personalized medicine: using a patient's biomarker "signature" to choose tailored treatments. For example, a patient with high inflammatory markers might in the future receive an anti-cytokine therapy, whereas one with purely hemodynamic stress markers gets aggressive diuresis and mechanical unloading. Current HF management is still largely "one size fits all" for certain HF subtypes, but biomarkers are paving the way for a more nuanced, phenotype-driven approach (Kennedy & Gaggin, 2023). Already, the distinction between HFrEF and HFpEF is partly biomarker-driven (HFpEF often has lower NP for the same pressure, higher inflammatory markers, etc.), and treatments differ between those groups.

In conclusion of this section, biomarkers have significant therapeutic implications: they can be used as indices of treatment efficacy (e.g., falling NT-proBNP), as triggers for therapy intensification (e.g., persistently high NP or ST2 prompting advanced therapy), and potentially as direct targets for novel treatments (e.g., drugs to lower galectin-3 or TMAO in the future). Clinicians should incorporate biomarker trends into the longitudinal care of HF patients, while recognizing the individual variability and not treating a number in isolation.

Emerging Biomarkers

The landscape of HF biomarkers continues to expand with advances in high-throughput "omics" technologies (genomics, proteomics, metabolomics, and transcriptomics). These approaches are enabling the discovery of novel biomarkers that could further refine diagnosis and prognosis, or reveal new therapeutic targets. Some promising emerging biomarkers and approaches include:

Genomic and Genetic Markers: Researchers are identifying genetic variants associated with HF development and outcomes. For example, certain polymorphisms in genes related to

the renin-angiotensin system, beta-adrenergic receptors, or natriuretic peptide pathways can influence an individual's risk of HF or response to therapy (Napoli et al., 2020). A notable example is the titin gene (TTN) truncating variants in dilated cardiomyopathy – while not a "biomarker" in the circulating sense, knowledge of such a mutation is prognostically important and may guide family screening. More broadly, polygenic risk scores for HF are being studied, which aggregate many genetic variants to predict who is at higher lifetime risk for HF (Stewart et al., 2019). In terms of gene expression, investigators have looked at myocardial gene expression profiles from endomyocardial biopsies to predict outcomes, but these are invasive. Instead, attention has turned to circulating RNAs.

MicroRNAs and Transcriptomic Markers: MicroRNAs (miRNAs) are small non-coding RNA molecules that regulate gene expression post-transcriptionally. They can be released into the circulation in microvesicles and have surprisingly stable presence in blood, making them potential biomarkers. Specific cardiac-associated miRNAs have been identified – for instance, miR-1, miR-133, miR-208, and miR-499 relate to cardiac muscle and injury. In HF, certain patterns of miRNAs are observed: some that promote hypertrophy or fibrosis are upregulated, and others are downregulated (Tijsen et al., 2012). A landmark study showed that a panel of circulating microRNAs could distinguish HF patients from controls and even identify symptomatic vs. asymptomatic left ventricular dysfunction (Tijsen et al., 2012). Some miRNAs, such as miR-423-5p, were proposed as diagnostic biomarkers for HF (Tijsen et al., 2012). Additionally, microRNA levels have prognostic significance; for example, elevated miR-210 and miR-30a were associated with higher mortality in HFrEF in some studies (Vegter et al., 2017). While no microRNA test is in clinical use yet, this area holds promise. The advantage is that miRNAs can reflect very specific biological processes (e.g., miR-21 from fibroblasts reflects

fibrosis, miR-146a from macrophages reflects inflammation). A panel of a few cardiac-specific miRNAs might one day augment or even replace some protein biomarkers for early detection of HF or for subclassifying HF etiology. Moreover, miRNAs themselves could be therapeutic targets (some trials are looking at antisense oligonucleotides to inhibit detrimental miRNAs in cardiovascular disease).

Proteomics and Novel Protein Biomarkers: Unbiased proteomic analysis of blood from HF patients versus controls has uncovered dozens of proteins not previously linked to HF. Modern mass spectrometry can quantify thousands of proteins simultaneously, and machine learning can pick out a combination that best classifies HF presence or predicts outcome. This has led to identification of candidates like **soluble urokinase plasminogen activator receptor (suPAR)**, which is elevated in HF and associated with outcomes (Eapen et al., 2015), or **growth hormone–releasing peptide** levels, etc. Many of these are still in exploratory phases. One notable new biomarker that has gained attention is **placental growth factor (PlGF)** – elevated PlGF was found in acute HF and predicted worse survival, reflecting vascular remodeling and angiogenesis pathways (van der Meer et al., 2019). **Adrenomedullin** we discussed; it came from proteomic interest and is now being tested as a therapeutic target with an antibody (Adrecizumab) in septic shock and possibly acute HF to see if outcomes improve by modulating that pathway (Voors et al., 2019). **Trail receptor-2 (TNFRSF10c)** is another novel protein from proteomics that correlated with mortality in chronic HF. The **Heart Failure Biomarker Network**, a multi-center initiative, has published results showing panels of novel proteins (including some uncharacterized ones) that strongly predict outcomes when combined with known markers (Ahmed et al., 2017). The challenge is validating and simplifying these into assays that clinicians can use. One commercial

multi-marker test (not yet standard) uses a score derived from multiple biomarkers such as ST2, galectin-3, and others. As proteomic technology becomes cheaper, we may see multi-analyte assays entering clinical practice – an analog in oncology is the multi-gene assays for cancer prognosis; in HF, multi-protein assays might give a more reliable risk score than any single marker.

Metabolomic Biomarkers: Metabolomics is the study of small molecules (metabolites) in blood or tissues. HF is accompanied by systemic metabolic changes – for example, there is a shift in myocardial energy substrate usage from fatty acids to glucose in advanced HF, and peripheral metabolic changes like insulin resistance are common. Metabolomic profiling in HF patients has identified certain metabolites linked to prognosis. A standout example is **trimethylamine N-oxide (TMAO)**, a metabolite produced by gut microbiota from dietary choline/carnitine. Elevated plasma TMAO has been associated with incident HF risk in population studies (Hazen et al., 2020) and with worse long-term outcomes in those with established HF (Li et al., 2020). A meta-analysis covering nearly 7,000 patients found that those with high TMAO had significantly higher mortality and HF hospitalization rates (Li et al., 2020). TMAO's prognostic value appears independent of kidney function (though renal impairment can raise TMAO too) and adds to traditional risk factors. This has spurred interest in the gut-heart axis: if high TMAO is bad, could dietary interventions (like reducing red meat) or drugs that alter gut flora reduce HF progression? Clinical trials are not yet there, but animal models suggest lowering TMAO can mitigate cardiac fibrosis and dysfunction (Hazen et al., 2020). Other metabolomic findings in HF include elevated **branched-chain amino acids** and altered lipid metabolites in HFpEF vs HFrEF. Some have proposed a "metabolic fingerprint" could differentiate HF subtypes or identify early HF before structural changes occur. For instance, a certain acylcarnitine

profile might signal early mitochondrial dysfunction in the myocardium. As these approaches develop, metabolite panels might become part of HF risk screening especially in high-risk populations (like diabetics) to catch subclinical HF development.

Omics Integration and Precision Medicine: The ultimate emerging concept is integrating multi-omics data – genomics, transcriptomics, proteomics, metabolomics – to achieve a comprehensive molecular characterization of each HF patient (Kennedy & Gaggin, 2023). This could potentially classify patients into distinct molecular phenotypes that respond differently to therapies. For example, one phenotype might be "inflammatory-cardiometabolic HF" (with high IL-6, CRP, TMAO, etc.) that might best respond to anti-inflammatory or SGLT2 inhibitor therapy, whereas another might be "fibro-proliferative HF" (high ST2, galectin-3, collagen markers) that might benefit from anti-fibrotic therapy or aggressive RAAS blockade. We are moving toward that direction, but significant research is needed to validate these phenotypes and find matching interventions.

From a biomarker standpoint, some novel markers on the horizon include: **sST2 genetic variants** (some people genetically have higher baseline ST2, which might modulate risk), **circulating collagen isoforms** that could precisely indicate myocardial fibrosis extent, **neuregulin-1 levels** as a marker of cardiomyocyte stress response, **microbiome-derived markers** beyond TMAO (like phenylacetylglutamine), and **machine learning-derived composite scores** using numerous features (for example, the AUC of a model using 50 biomarkers might outperform any set of 2–3 markers).

Another emerging area is **biomarkers in specific HF subsets** like amyloid cardiomyopathy – for instance, **serum free light chains** or **TTR stabilization assays** for transthyretin amyloidosis HF, and **genetic testing** for hypertrophic cardiomyopathy or channelopathies in HF. These help identify the

precise etiology which has therapeutic implications (e.g., tafamidis for transthyretin amyloid HF, which is guided by biomarker and imaging findings of amyloid).

It is important to emphasize that with so many potential biomarkers, there is a risk of information overload. The future likely lies in smart algorithms that combine biomarker data with clinical data (including data from devices or imaging) to produce a meaningful risk/diagnosis output. For example, an electronic health record might incorporate a patient's NP, troponin, CRP, GDF-15, etc. to flag a high risk of 1-year mortality prompting timely intervention.

In summary, emerging biomarkers from omics research promise to deepen our understanding of HF and improve clinical care by enabling early detection (perhaps even before symptoms by detecting molecular changes), precise risk stratification, and identification of novel therapeutic targets. While most are not yet ready for routine practice, ongoing studies are rapidly expanding the repertoire. It is conceivable that in the next decade, panels including some of these novel markers (e.g., a combination of genomic risk score, NP, hsTn, ST2, and TMAO) could become standard for a comprehensive HF assessment – aligning with the goal of **precision medicine** in cardiology (Kennedy & Gaggin, 2023).

Limitations and Future Directions

Despite the significant advances in biomarker research and their integration into HF care, there are important limitations to acknowledge, as well as opportunities for future improvements:

Biological Variability and Confounding: Many biomarkers lack disease-specificity. Conditions such as renal dysfunction, obesity, liver disease, infection, or age can alter biomarker levels independent of HF status (Anwaruddin et al., 2006; Bayes-Genis et al., 2007). For example, an elevated NT-proBNP in a patient with chronic kidney disease might overestimate HF severity due to

reduced clearance, whereas an obese patient could have deceptively low BNP despite advanced HF. Similarly, inflammatory markers (CRP, IL-6) may be high due to a comorbidity (e.g., arthritis or infection) rather than HF itself. This variability means clinicians must interpret results carefully and sometimes repeat measures or obtain a baseline when patients are in a compensated state to better judge changes. Future research may provide "adjusted" reference ranges (e.g., obesity-specific BNP thresholds) or combine markers to account for confounding (like using cystatin C alongside NP to account for renal effects) (Anwaruddin et al., 2006). Additionally, within-person variability (analytic and biologic) can be an issue – for instance, day-to-day NP levels can fluctuate with volume status. Establishing what constitutes a significant change (e.g., >30% change in NT-proBNP) is necessary to avoid overreacting to minor variations.

Lack of Universally Established Cutoffs for New Biomarkers: While BNP and troponin have well-known cutoffs (diagnostic and prognostic), newer markers like ST2, galectin-3, and others lack widely accepted thresholds for different clinical decisions. ST2 has a general 35 ng/mL risk threshold, but what about for initiating specific actions? There is no consensus like "if ST2 > X, do Y." The same goes for galectin-3 and others. This lack of standardization limits clinical uptake. Ongoing studies and registry data may help define such cutoffs or categories (low/intermediate/high risk ranges) that can be tied to management guidelines. Regulatory approval of biomarkers often lags behind research; ST2 and galectin-3 received approval for risk stratification, but it's up to clinicians to decide how to use that info. More guidance from professional societies on practical use (like the HFSA 2017 statement attempts to provide) will be needed (Chow et al., 2017).

Cost and Accessibility: Measuring multiple biomarkers can be costly and not all assays are widely available. Natriuretic peptides

and troponin are routine and relatively inexpensive. But tests like ST2, galectin-3, or novel multiplex panels can cost hundreds of dollars per test and may not be covered by insurance except in specialized cases. Cost-effectiveness is a major consideration for adopting new biomarkers. Studies have shown NP testing is cost-effective in acute dyspnea management (Mueller et al., 2004), but we lack such pharmacoeconomic data for many newer markers. If an emerging biomarker does not clearly change management or improve outcomes, its added cost is hard to justify in routine practice. Future technological advancements, such as point-of-care multi-biomarker devices or lab-on-chip platforms, could reduce costs and turnaround times. For example, a single drop of blood yielding NP, troponin, and CRP results in minutes is feasible with microfluidic technology – this could enhance ER and clinic decision-making if realized.

Clinical Utility and Outcome Impact: Perhaps the biggest limitation is translating biomarker knowledge into improved patient outcomes. A biomarker test by itself does not inherently make patients better; it must guide an intervention that improves outcomes. For well-established biomarkers, the interventions are clear (e.g., treat HF if NP is high, or treat CAD if troponin indicates MI). But for many newer markers, we don't yet have specific therapies to address the underlying process. For instance, knowing a patient's galectin-3 is high tells us they have a high risk fibrotic phenotype, but we don't currently have anti-fibrotic drugs proven to change that outcome in HF (traditional HF drugs may not specifically reduce galectin-3 levels as noted) (de Boer et al., 2013). This gap between prognostic markers and actionable therapy partly explains why multi-marker guided therapy trials have struggled. A future direction is developing therapies corresponding to biomarkers: e.g., if IL-6 is high, an IL-6 inhibitor; if TMAO is high, a gut microbiome intervention; if ST2 is high, perhaps an IL-33/ST2 pathway

modulator (though none exists yet). Precision medicine trials are needed where patients are stratified by a biomarker and then given a targeted therapy vs placebo to see if outcomes differ – akin to oncology trials. Some are ongoing (e.g., an IL-1 blocker trial recruited HF patients with high CRP to enrich for inflammation).

Integration with Clinical Workflow: Another practical limitation is clinician familiarity and workflow integration. It's relatively easy to incorporate an NP result into clinical practice now because everyone is trained to consider it. For newer biomarkers, many clinicians may not be as comfortable interpreting them. Widespread education and perhaps decision support tools (like EHR prompts) would be required for broad adoption. Additionally, the turnaround time for some specialized biomarkers can be slow (batch sent to reference labs), which reduces their utility for real-time decisions. Point-of-care testing development is a future direction to allow rapid biomarker panels in clinics/hospitals.

HF Phenotype Heterogeneity: HF is not one disease – HFrEF due to ischemic cardiomyopathy vs HFpEF due to amyloidosis vs right HF due to pulmonary hypertension are vastly different in pathophysiology. A single biomarker panel may not equally apply to all. In fact, some biomarkers are more useful in one context than another (e.g., IL-6 in HFpEF as noted, troponin in HFrEF). Thus, future HF management may require different biomarker strategies for different HF phenotypes. The 2021 ESC guidelines already recognize this by discussing biomarkers in HFpEF (where one must rely more on clinical judgment and multiple markers since NP can be lower) (McDonagh et al., 2021). Personalized biomarker profiling for each patient type is a direction – perhaps a HFpEF patient with obesity and diabetes gets a different panel (more metabolic and inflammatory markers) than a young HFrEF patient post-MI (who needs ischemia and remodeling markers).

Research and Validation: Finally, many emerging biomarkers need validation in large, diverse cohorts and ideally in randomized trials to prove that acting on them can improve patient outcomes. For example, does monitoring microRNAs or TMAO actually help if we have no direct therapy? Or if we did intervene (diet for TMAO), does it change hard endpoints? The next wave of clinical trials might involve biomarker-driven interventions (e.g., only treat patients above a biomarker threshold and see if outcome is better than treating all). Additionally, multi-center collaboration is required to standardize assays (one lab's normal range might differ from another's). The analytical precision of some assays (especially for cytokines or novel proteins) can be an issue – standardization and quality control will be essential to bring them to practice.

Future Directions: In light of these limitations, several future directions are evident. First, *refinement of multi-marker strategies* – using artificial intelligence and large datasets to determine the optimal combination of markers that yields maximum prognostic/diagnostic accuracy with minimal redundancy (Kennedy & Gaggin, 2023). Second, *development of targeted therapies* informed by biomarkers – for example, trials of anti-fibrotics (like pirfenidone or novel agents) in patients with high ST2/galectin-3, or anti-inflammatory drugs in those with high CRP/IL-6, or gut microbiome interventions in those with high TMAO. If these trials succeed, they will directly link biomarker levels to therapy decisions. Third, *point-of-care and home biomarker monitoring*: Just as implantable devices now monitor pulmonary pressure, one could envision a future home finger-prick test or wearable that periodically measures NT-proBNP or other markers, alerting patients and providers to early decompensation – akin to a "lab test equivalent" of a home glucose monitor for HF (Wettersten, 2021). This could enable preemptive outpatient interventions and reduce hospitalizations. Some studies (like TIM-HF2) have used remote NP

monitoring as part of telemanagement with positive results, indicating potential here. Fourth, *integration withdigital phenotyping*: combining biomarkers with data from wearable sensors (heart rate, activity, etc.) might give an even fuller picture of HF status daily.

Lastly, as our knowledge grows, *guideline incorporation* will follow. We can expect future HF guidelines to possibly include recommendations like: "It may be useful to measure sST2 or galectin-3 in patients with chronic HF to aid in risk stratification (Class IIb)" or in HFpEF: "Consider measuring inflammatory biomarkers as part of the diagnostic workup." Over time, as evidence solidifies, this may strengthen.

In conclusion of limitations/future: While current biomarkers greatly enhance HF care, each has constraints, and none alone is a magic bullet. The future likely lies in **combining biomarkers with each other and with clinical data to create robust predictive models**, and in tailoring therapies based on a patient's biomarker profile. Addressing cost, standardization, and demonstrating clinical outcome benefit will be key to broader implementation of the rich array of biomarkers emerging from research.

Conclusion

Biomarkers have revolutionized the approach to heart failure by providing quantitative measures of the complex pathophysiological derangements that characterize this syndrome. In this chapter, we have reviewed the major biomarkers in HF, encompassing those in routine clinical use – notably the natriuretic peptides and cardiac troponins – as well as a spectrum of emerging markers reflecting inflammation, oxidative stress, fibrosis, renal function, and novel molecular pathways. For both chronic HF and acute decompensated HF, biomarkers enhance diagnostic accuracy, allowing earlier and more confident identification of HF among

patients with ambiguous presentations. They also offer powerful prognostic insights: levels of BNP/NT-proBNP, troponin, ST2, galectin-3, IL-6, cystatin C, and others have all been linked to outcomes, enabling clinicians to stratify risk and personalize monitoring intensity. Biomarker trends can signal whether a patient's HF is stabilizing or deteriorating, and in some cases suggest when to escalate therapy or consider advanced interventions.

Therapeutically, while the era of strictly biomarker-guided HF therapy is still evolving, biomarkers already inform day-to-day management – for instance, guiding diuresis (with NP levels), screening for myocardial ischemia (troponin), and addressing co-morbid factors like iron deficiency or renal dysfunction. Ongoing research is likely to translate certain biomarkers into direct therapeutic targets, paving the way for precision medicine in HF where treatment is tailored to the patient's dominant pathological pathway (be it neurohormonal, inflammatory, metabolic, or fibrotic). The incorporation of multi-marker strategies and omics-based biomarkers holds promise for earlier detection of subclinical HF, differentiation of HF phenotypes (e.g., HFrEF vs HFpEF), and more nuanced risk prediction than ever before.

However, it is equally important to recognize the limitations of current biomarkers – issues of specificity, variability, and cost – and to ensure that biomarker testing is used thoughtfully, in conjunction with clinical judgment and imaging. The future of HF care will likely see an expanded panel of biomarkers used in concert, integrated via computational tools to aid clinical decision-making. As therapies become more targeted to underlying mechanisms, biomarkers will play a critical role in identifying the right patients for the right treatment at the right time.

In summary, biomarkers have become indispensable in modern HF management for diagnosis, prognosis, and increasingly for guiding therapy. They provide objective metrics in a syndrome

that was once assessed only by clinical acumen, thereby improving accuracy and confidence in decision-making. The ultimate goal moving forward is that through biomarkers and precision approaches, we will achieve better outcomes – reducing hospitalizations and mortality and improving the quality of life for patients living with heart failure. Continued research and clinical trials are essential to validate emerging biomarkers and ensure that their implementation tangibly benefits patients. The trajectory of current evidence suggests that we are on the cusp of a new era in heart failure care, one where a multi-dimensional biomarker profile will be as routine as an electrocardiogram, and where therapies will be increasingly personalized based on the rich information that these biomarkers provide. This convergence of clinical insight and molecular data heralds a future of more precise and effective heart failure management.

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BÖLÜM 4

CARDİOVASCULAR DİSEASE PREVENTİON: BEYOND LDL – FOCUS ON TRİGLYCERİDES, LP(A), AND INFLAMMATİON

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Introduction

Cardiovascular disease (CVD) prevention has historically centered on lowering low-density lipoprotein cholesterol (LDL-C), yielding major reductions in atherosclerotic cardiovascular disease (ASCVD) events. Landmark clinical trials and meta-analyses confirm that each 1 mmol/L (~39 mg/dL) reduction in LDL-C confers roughly a 20–22% relative risk reduction in ASCVD events, with no apparent lower limit of LDL-C beyond which benefit ceases (Baigent et al., 2010; Silverman et al., 2016). Aggressive LDL-C lowering – through high-intensity statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors – has thus become standard in high-risk patients (Grundy et al., 2019). Yet, even when LDL-C is reduced to very low levels (< 1.0 mmol/L or < 40 mg/dL), a substantial "residual risk" of CVD events persists (Sabatine et al., 2017; Schwartz et al., 2018). For example, in the

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FOURIER and ODYSSEY Outcomes trials of PCSK9 inhibitors, 5–10% of patients still experienced major cardiovascular events over ~3 years despite LDL-C levels near 0.5–0.7 mmol/L (20–30 mg/dL) (Sabatine et al., 2017; Schwartz et al., 2018). Similarly, in earlier statin trials, a considerable proportion of patients had recurrent events even after maximal LDL-C reduction (Ridker et al., 2016). This residual risk has prompted a critical appraisal of non-LDL factors that contribute to ASCVD. In particular, attention has shifted to triglyceride-rich lipoproteins, lipoprotein(a), and chronic inflammation as key players in atherogenesis that are not addressed by LDL-centric therapy (Bashir et al., 2024). This chapter provides an in-depth review of these factors "beyond LDL," discussing their roles in CVD pathophysiology, evidence from clinical trials and guidelines, population variations, and emerging strategies for comprehensive risk reduction.

Beyond LDL Cholesterol: Residual Risk and New Targets

While LDL-C remains a primary driver of atherosclerosis, it is now evident that other lipid and inflammatory pathways significantly influence risk. The concept of residual cardiovascular risk refers to the risk remaining after optimal control of LDL-C and other traditional factors. Contributors to residual risk include triglyceride-rich lipoproteins (e.g., very low-density and intermediate-density lipoproteins), elevated lipoprotein(a) [Lp(a)], systemic inflammation, as well as factors like hypertension, diabetes, and thrombosis (Libby & Everett, 2019). Many of these factors are interrelated; for instance, metabolic syndrome and insulin resistance promote both hypertriglyceridemia and a pro-inflammatory state. Importantly, LDL-centric measures such as non-HDL cholesterol or apolipoprotein B (apoB) can better capture the total atherogenic particle burden (which includes Lp(a) and triglyceride-rich remnants) and have been shown to predict ASCVD risk more accurately than LDL-C alone (Sniderman et al., 2019;

Mach et al., 2020). Patients with discordantly high apoB relative to LDL-C (often due to high triglycerides or Lp(a)) are at elevated risk that would be underestimated by LDL-C measurement (Sniderman et al., 2019). Thus, contemporary guidelines now emphasize assessing non-HDL-C or apoB as secondary targets, especially in individuals with hypertriglyceridemia or high Lp(a) (Mach et al., 2020; Grundy et al., 2019). Recognizing and addressing these "beyond LDL" factors is critical to further reduce CVD incidence. In the following sections, we examine three major frontiers: triglycerides and triglyceride-rich lipoproteins, Lp(a), and inflammation.

Triglycerides and Atherogenic Remnant Lipoproteins

Triglycerides (TGs) are carried in the bloodstream by triglyceride-rich lipoproteins, namely chylomicrons (post-prandially) and very low-density lipoproteins (VLDL), as well as their remnants (remnant lipoproteins such as intermediate-density lipoproteins, IDL). Historically, hypertriglyceridemia has been viewed with uncertainty as a risk factor because of complex intercorrelations with other lipids (especially high-density lipoprotein cholesterol, HDL-C) and metabolic variables. Normal fasting triglyceride levels are typically defined as <150 mg/dL (<1.7 mmol/L), with levels of 150–199 mg/dL considered borderline elevated, 200–499 mg/dL high, and ≥500 mg/dL very high (Virani et al., 2021). Severe hypertriglyceridemia (≥ 1000 mg/dL) can precipitate acute pancreatitis and warrants urgent management, but even moderate elevations (150–499 mg/dL) are now recognized as contributory to CVD risk (Grundy et al., 2019; Mach et al., 2020). It is the cholesterol content in triglyceride-rich remnant particles (often termed "remnant cholesterol") that is highly atherogenic, as these remnants can penetrate the arterial wall and promote foam cell formation much like LDL particles do (Varbo et al., 2013). Unlike LDL, which is typically enriched in cholesterol, triglyceride-rich

VLDL/IDL particles carry less cholesterol per particle but can exist in large numbers in certain metabolic states. Elevated triglycerides often coexist with low HDL-C – a pattern characteristic of insulin resistance and metabolic syndrome – complicating the isolation of triglyceride-specific risk. Nonetheless, extensive evidence now supports triglyceride-rich lipoproteins as independent causal factors in ASCVD.

Epidemiology and Causal Inference for Triglycerides

Large epidemiological studies have long shown an association between higher plasma triglyceride levels and increased risk of coronary heart disease (CHD). In a meta-analysis of 29 prospective studies encompassing >260,000 participants, those in the highest quintile of triglycerides had a significantly greater risk of CHD events, even after adjusting for HDL-C (Sarwar et al., 2007). Every 1 mmol/L (~88.5 mg/dL) increase in triglycerides was associated with ~30% higher CHD risk in that analysis (Sarwar et al., 2007). However, because lifestyle factors and other lipid variables confound these relationships, attention turned to genetic evidence to clarify causality. Mendelian randomization studies – which use genetic variants as instruments – have provided compelling support that triglyceride-rich lipoproteins are causally related to ASCVD risk. For example, loss-of-function mutations in APOC3 (a gene that raises triglyceride levels by inhibiting lipoprotein lipase) lead to lifelong lower triglycerides and associate with reduced coronary disease risk, suggesting a protective effect of low TGs (Jørgensen et al., 2014). Conversely, variants that raise triglyceride levels (or the number of VLDL particles) confer higher CVD risk proportional to the lifelong TG elevation (Ference et al., 2019). A recent analysis of the UK Biobank estimated that triglyceride-rich remnant lipoproteins may be even more atherogenic on a per-particle basis than LDL, highlighting the importance of remnant cholesterol as a driver of risk (Björnson et al., 2023). These

lines of evidence align in identifying triglyceride-rich lipoproteins as an important therapeutic target, especially in the context of the prevalent cardiometabolic disorders of modern societies (obesity and type 2 diabetes). Indeed, the cluster of high TG, low HDL, and small dense LDL seen in metabolic syndrome is strongly associated with ASCVD, sometimes termed "atherogenic dyslipidemia" (Grundy et al., 2005). Notably, certain ethnic groups, such as South Asians, exhibit this atherogenic dyslipidemia pattern with high frequency – partly explaining their elevated premature CVD risk despite often unremarkable LDL-C levels (Shah et al., 2018). This underscores the need for a broader lipid risk assessment beyond LDL in diverse populations.

Clinical Trial Evidence: Triglyceride Lowering and Cardiovascular Outcomes

Despite clear evidence that elevated triglyceride-rich lipoproteins are associated with ASCVD, clinical trials of triglyceride-lowering therapies have yielded mixed results in terms of reducing cardiovascular events. Key intervention strategies have included fibrate drugs, niacin (vitamin B_3), and omega-3 fatty acid supplements – often tested on a background of statin therapy in modern trials. Table 1 summarizes major clinical trials targeting triglycerides or related dyslipidemia and their outcomes.

Fibrate trials: Fibrates (PPAR-α agonists) lower triglycerides by 30–50% and raise HDL-C modestly. Early fibrate trials in the pre-statin era showed some benefits. The Helsinki Heart Study (1987) found gemfibrozil significantly reduced CHD events in dyslipidemic middle-aged men (Frick et al., 1987). The VA-HIT trial (1999) in men with established CHD and low HDL-C also showed gemfibrozil reduced non-fatal MI by 22% (Rubins et al., 1999). However, in the statin era, fibrates added to statins have not demonstrated clear benefits for broad populations. The ACCORD-

Lipid trial (2010) tested fenofibrate + statin vs. statin alone in over 5,000 patients with type 2 diabetes; it found no significant reduction in CVD events with fenofibrate, except a suggested benefit in a subgroup with high baseline TG (≥204 mg/dL) and low HDL-C (≤34 mg/dL) (ACCORD Study Group, 2010). Similarly, the FIELD trial (2005) of fenofibrate in diabetics (many not on statins) showed no significant primary outcome benefit (Keech et al., 2005). Most recently, the PROMINENT trial (2022) evaluated pemafibrate, a novel fibrate, in ~10,000 statin-treated patients with type 2 diabetes, TG 200–499 mg/dL and low HDL-C. Pemafibrate lowered triglycerides by ~30% but did **not** reduce cardiovascular events compared to placebo (3.5% vs 3.6% event rate over 3+ years; p=0.67) (Das Pradhan et al., 2022). Intriguingly, pemafibrate slightly increased LDL-C and apoB levels, and was associated with higher rates of adverse effects like venous thromboembolism (Das Pradhan et al., 2022). The PROMINENT results, consistent with prior fibrate trials, indicate that routine fibrate therapy on top of statins provides no incremental ASCVD risk reduction, leading experts to conclude that fibrates should not be routinely used for cardiovascular prevention (Bavry & Bhatt, 2023). An exception may be considered in select cases such as severe hypertriglyceridemia at risk for pancreatitis, or possibly in patients with pronounced atherogenic dyslipidemia (high TG/low HDL) who cannot achieve non-HDL-C goals by other means – though even this is debatable after PROMINENT.

Niacin trials: Niacin can lower triglycerides by 20–30%, raise HDL-C substantially, and modestly lower LDL-C/Lp(a). Earlier studies suggested niacin monotherapy reduced CHD events (Coronary Drug Project, 1975). However, two large modern trials of niacin added to statin therapy failed to show benefit. The AIM-HIGH trial (2011) tested extended-release niacin in patients with CVD, low HDL and controlled LDL; it was stopped early for futility as niacin

did not reduce events (Boden et al., 2011). Similarly, HPS2-THRIVE (2014), which added niacin/laropiprant to statins in ~25,000 patients, showed no ASCVD benefit but significant adverse effects (flushing, infections, diabetes exacerbation, bleeding) (Landray et al., 2014). Notably, niacin does lower Lp(a) by ~20%, but any theoretical benefit was outweighed by harms in these trials. As a result, niacin is no longer recommended for routine CVD prevention (Grundy et al., 2019).

Omega-3 fatty acids: Marine-derived omega-3 fatty acids (EPA and DHA) in high doses can lower triglycerides by 20–30%. Trials of low-dose fish oil (e.g., 1 g/day) in unselected populations have largely been negative for CV prevention (Manson et al., 2019; ASCEND Study Collaborative Group, 2018). However, a breakthrough came with trials of high-dose, pure EPA. The JELIS trial (2007) in Japan (using 1.8 g/day EPA added to statin) showed a 19% reduction in major coronary events, particularly in a subgroup with elevated TG and low HDL (Yokoyama et al., 2007). This benefit was confirmed in the multinational REDUCE-IT trial (Bhatt et al., 2019). REDUCE-IT enrolled over 8,000 high-risk patients (71% with CVD, others with diabetes) who had TG 135–499 mg/dL despite statin therapy and relatively well-controlled LDL-C (median ~75 mg/dL). Patients were randomized to **icosapent ethyl** (a purified EPA at 4 g/day) vs placebo (mineral oil). After 5 years, the icosapent group saw a 25% relative reduction in major cardiovascular events (composite of CV death, MI, stroke, revascularization, unstable angina) compared to placebo (hazard ratio 0.75, $p<0.001$) (Bhatt et al., 2019). Notably, median TG levels fell by 19% in the EPA group (to ~200 mg/dL) and rose slightly in the placebo group; EPA also significantly lowered markers of inflammation and possibly plaque instability (Bhatt et al., 2019). REDUCE-IT was a landmark trial establishing icosapent ethyl as an effective adjunct therapy in patients with elevated TG on statins, and it has been incorporated

into guidelines (Visseren et al., 2021). In contrast, the contemporaneous STRENGTH trial (2020), which tested a 4 g/day combination of EPA and DHA in a similar population, was neutral – showing no CV benefit (Nicholls et al., 2020). The discrepant outcomes between REDUCE-IT and STRENGTH have spurred debate. Possible explanations include the choice of placebo (mineral oil in REDUCE-IT, which some argue might have worsened outcomes in the control group, though evidence is mixed) and the different formulations (EPA-only in REDUCE-IT vs EPA+DHA in STRENGTH, with some data suggesting DHA could counteract certain benefits of EPA or that EPA's high achieved blood levels were critical) (Nicholls et al., 2020; Bhatt et al., 2020). Regardless, icosapent ethyl is now an evidence-based therapy for triglyceride-related residual risk. It is worth emphasizing that these benefits likely extend beyond triglyceride lowering per se, potentially involving EPA's pleiotropic effects on plaque stabilization, membrane composition, anti-inflammation, and antithrombotic pathways.

Lifestyle and other therapies: Lifestyle interventions—weight loss, dietary modifications, and increased physical activity—remain foundational for managing elevated triglycerides. Low-carbohydrate and Mediterranean-style diets can significantly reduce TG levels and improve the overall metabolic profile (Joshi et al., 2021). Alcohol moderation (as excessive intake can raise TGs) and optimized glycemic control in diabetes are also important (Virani et al., 2021). Other emerging therapies include inhibitors of apolipoprotein C-III (apoC-III) and angiopoietin-like protein 3 (ANGPTL3), which are being tested in severe hypertriglyceridemia and familial chylomicronemia. These novel antisense oligonucleotide or RNAi agents can dramatically lower triglycerides by enhancing lipoprotein lipase activity or clearance of TG-rich particles (Taha et al., 2020). While primarily aimed at pancreatitis

prevention in extreme hypertriglyceridemia, such agents (e.g., volanesorsen for apoC-III, evinacumab for ANGPTL3) could have implications for ASCVD risk if studied in broader populations. Currently, however, there are no outcomes trials yet demonstrating that targeting these pathways reduces CVD events.

Taken together, the evidence suggests triglycerides are an important marker and mediator of risk, but simply lowering triglyceride numbers is not guaranteed to improve outcomes unless the therapy also favorably modifies the atherogenic remnants or underlying process. The success of icosapent ethyl indicates that certain patients (those with residual hypertriglyceridemia despite statins, often accompanied by other risk factors) can indeed benefit from triglyceride-targeted treatment. By contrast, fibrate and niacin trials underscore that focusing on HDL-C raising or nonspecific TG lowering without addressing apoB-containing particle burden or inflammation may fail to translate into benefits. This nuanced understanding is influencing clinical practice.

Guidelines and Recommendations on Triglyceride Management

Both European and American guidelines have updated their stances on managing hypertriglyceridemia in light of recent evidence. The 2018 AHA/ACC Cholesterol Guideline identified triglycerides ≥175 mg/dL (persistent, fasting) as a risk-enhancing factor for ASCVD in primary prevention – meaning that if a patient's 10-year risk is borderline, an elevated TG can tilt the decision towards initiating or intensifying therapy (Grundy et al., 2019). The guideline emphasizes lifestyle optimization for all patients with TG elevation. Pharmacologically, statins remain first-line even for those with high TG, given their robust risk reduction and modest TG-lowering effect. For severe hypertriglyceridemia (≥500 mg/dL), fibrates or high-dose omega-3 fatty acids are recommended primarily to reduce pancreatitis risk (Grundy et al., 2019; Virani et

al., 2021). Importantly, the ACC issued a 2021 Expert Consensus Decision Pathway focusing on persistent hypertriglyceridemia (Virani et al., 2021). This consensus recommends: ensure secondary causes are managed (e.g., uncontrolled diabetes, hypothyroidism, medications), reinforce diet (very low-fat diet if TG >1000), and prioritize achieving LDL-C targets with statins. In patients with ASCVD or at high-risk with TG 135–499 mg/dL despite statin, the ACC pathway endorses consideration of adding icosapent ethyl 4 g/day (Virani et al., 2021). Icosapent ethyl received a Class I recommendation in the 2019 American Diabetes Association guidelines for CV risk reduction in diabetics with elevated TG, and has been approved by the FDA for CVD risk reduction in those with TG >150 mg/dL on statin (Bhatt et al., 2019). Meanwhile, fibrates are not recommended solely for ASCVD prevention on top of statins, in alignment with trial evidence (Das Pradhan et al., 2022; Virani et al., 2021).

The 2019 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) Guidelines similarly advocate for focusing on non-HDL-C or apoB to assess and manage risk in patients with high TG (Mach et al., 2020). These guidelines recommend considering icosapent ethyl in high-risk patients with TG 1.5–5.6 mmol/L (~135–500 mg/dL) despite statins (Class IIa), acknowledging the REDUCE-IT results (Visseren et al., 2021). For severe hypertriglyceridemia, ESC/EAS advises fibrate or omega-3 to lower TG and prevent pancreatitis (Mach et al., 2020). Both US and European guidelines stress that any decision to treat moderate hypertriglyceridemia should be made in the context of overall risk and after optimizing LDL-C management. They also note that glycemic control (in diabetes) and abstinence from alcohol can dramatically improve triglyceride levels.

In summary, triglycerides have emerged from the shadow of LDL as both a marker of residual risk and a therapeutic target in

selected patients. The focus is not on triglycerides in isolation, but on the atherogenic remnant lipoproteins and metabolic milieu they represent. Current guidelines reflect a more nuanced and evidence-driven approach: lifestyle first; then for patients with high residual TG and high risk, adding icosapent ethyl is evidence-based, whereas adding fibrates or niacin to statins is generally not. The overall goal is to reduce the total burden of apoB-containing lipoproteins (LDL + remnants) and address underlying metabolic drivers.

Table 1. Major Clinical Trials Targeting Triglycerides or Atherogenic Dyslipidemia and Effects on Cardiovascular Outcomes

Trial (Year)	Population (key inclusion)	Intervention vs. Control	Triglyceride Change	Outcome Result (ASCVD events)
Helsinki Heart Study (1987) (Frick et al., 1987)	4,081 dyslipidemic men (no CHD)	Gemfibrozil vs. placebo	TG ↓~43%; HDL ↑10%	CHD events ↓ 34% ($p<0.02$); first trial showing fibrate benefit in primary prevention.
VA-HIT (1999) (Rubins et al., 1999)	2,531 men with CHD, low HDL (<40)	Gemfibrozil vs. placebo	TG ↓31%; HDL ↑6%	Non-fatal MI or CHD death ↓ 22% ($p=0.006$). No change in total mortality.
FIELD (2005) (Keech et al., 2005)	9,795 type 2 diabetics (mixed statin use)	Fenofibrate vs. placebo	TG ↓~30%; HDL ↑5%	No sig. reduction in CAD events ($p=0.16$); ↓ microvascular events. Some benefit in high TG subgroup.

ACCORD-Lipid (2010) (ACCORD, 2010)	5,518 type 2 diabetics on statin	Fenofibrate + statin vs. statin	TG ↓~20% (baseline 162)	No overall ASCVD event reduction (p=0.32); subgroup with TG ≥204 & HDL ≤34 had 31%↓ events (interaction p=0.057).
AIM-HIGH (2011) (Boden et al., 2011)	3,414 CVD patients, low HDL, on statin	Niacin ER + statin vs. statin	TG ↓28%; HDL ↑25%	Stopped early – no benefit on ASCVD events; trend toward more ischemic strokes with niacin.
HPS2-THRIVE (2014) (Landray et al., 2014)	25,673 high-risk patients on statin	Niacin/laropiprant vs. placebo	TG ↓36%; HDL ↑14%	No ASCVD event reduction; niacin arm had more serious adverse effects (diabetes, bleeding, etc.).
JELIS (2007) (Yokoyama et al., 2007)	18,645 Japanese hypercholesterolemic patients	EPA 1.8 g + low-dose statin vs. statin	TG ↓5% (baseline ~150)	Major CHD events ↓ 19% (p=0.011). Largest benefit in subgroup with TG ≥150 & HDL <40 (~53% risk reduction).
REDUCE-IT (2019) (Bhatt et al., 2019)	8,179 high-risk (CVD or diabetes) with TG 135–499 on statin	**Icosapent ethyl 4 g/day** vs. placebo (mineral oil)	TG ↓19%; LDL ~unchanged	**MACE↓ 25%** (5-pt composite: 17.2% vs 22.0%,

				p<0.001). CV death ↓ 20%. Established EPA as beneficial therapy.
STRENGTH (2020) (Nicholls et al., 2020)	13,078 high-risk patients with TG ≥180 on statin	Omega-3 carboxylate 4 g (EPA+DHA) vs. placebo (corn oil)	TG ↓19% (EPA+DHA)	**No difference** in MACE (primary endpoint ~12% in both groups, p=0.84). Trial stopped early for futility.
PROMINENT (2022) (Das Pradhan et al., 2022)	10,497 type 2 diabetics, TG 200–499, HDL ≤40 on statin	Pemafibrate vs. placebo	TG ↓31%; HDL ↑5%	**No difference** in MACE (3.4% vs 3.5%, p=0.67). Pemafibrate increased VTE and renal events. No CV benefit, aligning with prior fibrate trials.

Abbreviations: CHD – coronary heart disease; CVD – cardiovascular disease; MACE – major adverse cardiovascular events (definitions vary by trial, generally includes CV death, myocardial infarction, stroke, etc.); MI – myocardial infarction; TG – triglycerides; HDL – high-density lipoprotein cholesterol; ↓ – decrease; ER – extended release.

(Table compiled from trial publications as cited above.)

Lipoprotein(a): An Elusive but Important Risk Factor

Lipoprotein(a), often abbreviated as Lp(a), has gained recognition as a significant independent risk factor for ASCVD, representing a pathway entirely separate from LDL-C, HDL-C, or triglycerides. Lp(a) consists of an LDL-like particle (containing an apoB100 core) attached via a disulfide bond to a distinctive apolipoprotein(a) [apo(a)] molecule. The apo(a) protein has a kringle-domain structure analogous to plasminogen, which bestows prothrombotic and proinflammatory properties. The plasma level of Lp(a) is >90% genetically determined, primarily by variants in the LPA gene that affect the number of kringle IV repeats in apo(a). This genetic architecture leads to enormous inter-individual variability in Lp(a) levels – over 1000-fold range – with skewed distribution (most people have low levels, but a minority have very high levels) (Kronenberg et al., 2022). Lp(a) levels are measured in mg/dL of Lp(a) cholesterol or in nmol/L of Lp(a) particles; levels above ~50 mg/dL (≈ 100–125 nmol/L) are considered elevated and have been associated with increased CVD risk (Tsimikas, 2017; Grundy et al., 2019).

Mechanisms and Pathophysiology of Lp(a)

Several mechanisms make Lp(a) atherogenic and thrombogenic. Because Lp(a) contains an LDL-like particle, it can penetrate the endothelium and deliver cholesterol to the arterial intima, contributing to foam cell formation and plaque development much like LDL does. In addition, the unique apo(a) component interferes with fibrinolysis: apo(a) is structurally similar to plasminogen but biologically inactive in clot lysis, thus Lp(a) may compete with plasminogen and promote thrombosis on atherosclerotic plaques (Berg et al., 2019). Lp(a) also carries oxidized phospholipids, which are pro-inflammatory and augment vascular inflammation (Tsimikas, 2017). This combination of pro-atherogenic, pro-inflammatory, and prothrombotic effects likely explains why elevated Lp(a) is associated not only with higher risk

of myocardial infarction and stroke, but also with calcific aortic valve stenosis (Lp(a) is now recognized as a causal risk factor for aortic stenosis via deposition of oxidized phospholipids in the valve leaflets) (Capoulade et al., 2019). Importantly, Lp(a) levels are *not* significantly influenced by lifestyle (diet and exercise have minimal effect) and are only modestly affected by common medications. Statin therapy has little to no effect or may even raise Lp(a) slightly (by ~10%), while PCSK9 inhibitors reduce Lp(a) by about 20–30% as an off-target effect (Schwartz et al., 2018). Niacin can lower Lp(a) by ~20% and estrogen therapy also reduces Lp(a), but neither are acceptable solely for this purpose given other risks. Therefore, Lp(a) is largely a fixed, inherited risk factor across one's lifespan – which is why guidelines emphasize measuring it at least once.

Epidemiology and Regional/Ethnic Variations

Elevated Lp(a) is common: globally, an estimated 20% of people have Lp(a) levels above the risk-threshold of 50 mg/dL, though prevalence varies by ethnicity (Kronenberg et al., 2022). Striking ethnic differences in Lp(a) levels have been documented. Individuals of African ancestry have the highest Lp(a) levels on average, with median levels around 2–3 times that of Europeans or East Asians (Mehta et al., 2022). For example, in the UK Biobank study the median Lp(a) concentration was ~75 nmol/L in Black individuals, ~30 nmol/L in South Asians, ~19 nmol/L in Whites, and ~16 nmol/L in Chinese participants (Mehta et al., 2022; Thanassoulis et al., 2013). Correspondingly, the frequency of very elevated Lp(a) (>50 mg/dL) ranges from as low as ~5% in East Asian populations up to ~20–30% in those of African descent (Enas et al., 1997; Virani et al., 2022). These differences are attributed to the distribution of LPA gene variants; African populations tend to have smaller apo(a) isoforms that drive higher Lp(a) levels. Importantly, while baseline levels differ, the relative risk associated with high Lp(a) appears present across all ethnic groups studied (Mehta et al., 2022).

However, because background risk and competing factors vary, the *absolute* risk conferred by a given Lp(a) level might not be identical in every population. One challenge is determining uniform risk thresholds applicable to diverse groups. For instance, some have suggested higher "normal" thresholds for African Americans given their overall higher Lp(a) distribution, but current clinical thresholds (≈30 mg/dL for moderate risk, 50 mg/dL for high risk, 180 mg/dL for extremely high risk) are generally used across populations (Kronenberg et al., 2022). The key point remains that Lp(a) is a significant inherited risk factor in all populations, and particularly high levels (>~90th percentile) portend a substantially elevated lifetime risk of ASCVD.

From a global perspective, the contribution of Lp(a) to CVD risk is believed to be greater in South Asians and African ancestry groups partly because of their higher prevalence of elevation, whereas East Asian populations have a smaller burden of Lp(a)-mediated risk (Lee et al., 2017). Nonetheless, factors like LDL-C, hypertension, and diabetes often dominate risk in developing countries, and Lp(a) may be more impactful in those who otherwise achieve LDL-C control (as is increasingly the case in Western cohorts). It's also worth noting regional guideline differences: for example, the Canadian guidelines explicitly flag South Asian ethnicity as a condition where Lp(a) measurement is particularly useful (Pearson et al., 2021). Additionally, because Lp(a) is largely genetically determined, familial patterns are seen – elevations often cluster in families independent of other lipid traits. This has implications for cascade screening: identifying a person with very high Lp(a) should prompt measuring Lp(a) in first-degree relatives, as recommended by some guidelines (Wilson et al., 2019).

Clinical Impact: Lp(a) and ASCVD Risk

The link between Lp(a) and ASCVD has been demonstrated in numerous epidemiological studies and meta-analyses. A 2009 meta-analysis of 36 studies (126,000 participants) found that those in the top vs. bottom third of Lp(a) had about a 70% higher risk of CHD (Erqou et al., 2009). More recent large-scale analyses, including the Emerging Risk Factors Collaboration and UK Biobank studies, confirm a continuous, approximately log-linear relationship between Lp(a) concentration and ASCVD risk (Di Angelantonio et al., 2012; Kronenberg et al., 2022). For example, an Lp(a) level in the top 5% (>~90–120 mg/dL or >~250 nmol/L) can confer over 2-fold higher risk of heart attack compared to someone with very low Lp(a) (Kamstrup et al., 2009). Mendelian randomization analyses further bolster causality: carrying variants that raise Lp(a) is associated with higher rates of MI and aortic stenosis, analogous in magnitude to the effect of lifelong elevated LDL-C of a similar extent (Thanassoulis et al., 2013). Thus, the consensus is that Lp(a) is an independent, genetically determined, causal risk factor for ASCVD.

Clinically, high Lp(a) contributes to what is often termed "residual cholesterol risk" or "LDL-C–independent risk." Patients with high Lp(a) may present with premature cardiovascular events despite having acceptable LDL-C levels, or they may have more aggressive progression of atherosclerosis than expected. A particularly extreme scenario is when a patient has both familial hypercholesterolemia (high LDL from birth) and high Lp(a), which multiplies risk; indeed, the ESC/EAS considers Lp(a) >180 mg/dL (~430 nmol/L) as a "risk equivalent" similar to heterozygous FH, implying very high lifetime risk (Mach et al., 2020; Kronenberg et al., 2022). Elevated Lp(a) also helps explain some cases of early ASCVD in the absence of other risk factors, as well as cases of stent restenosis and vein graft failure (since Lp(a) can promote a

prothrombotic state). Additionally, as noted, high Lp(a) is one of the strongest risk factors for calcific aortic stenosis, for which currently the only treatment is valve replacement (Capoulade et al., 2019).

For risk stratification, an important consideration is that standard lipid panels do not capture Lp(a). An individual with an LDL-C measured at 100 mg/dL might actually have a significant portion of that cholesterol carried by Lp(a) particles (which are counted as LDL by standard Friedewald calculation). For example, if Lp(a) is 50 mg/dL, the "true" LDL-C (from LDL particles) might be only ~70–80 mg/dL. This is why apoB or LDL particle number can be useful – each Lp(a) has an apoB, so an elevated Lp(a) raises apoB without raising LDL-C equivalently. In patients who have unexpectedly high apoB or non-HDL-C relative to LDL-C, one should suspect high Lp(a) as a cause (Sniderman et al., 2019). In fact, a recent analysis of the ODYSSEY Outcomes trial data suggested that on-treatment apoB was a better predictor of residual risk than LDL-C, partly due to undetected Lp(a) and VLDL contributions (Hagström et al., 2019). Thus, measuring Lp(a) provides incremental information beyond the standard lipid profile.

Screening and Guidelines for Lp(a)

Given the above, numerous guidelines now advocate for at least one-time measurement of Lp(a) in adults. The 2019 ESC/EAS dyslipidemia guidelines recommend measuring Lp(a) in every adult at least once in their lifetime, ideally at the time of initial lipid evaluation (Mach et al., 2020). This is to identify those with very high inherited Lp(a) levels who would benefit from risk factor intensification. The guideline specifically notes that Lp(a) >180 mg/dL is associated with a ~3–4-fold increase in ASCVD risk (over a lifetime) and is analogous to familial hypercholesterolemia in risk (Mach et al., 2020). The European Atherosclerosis Society 2022 consensus statement reinforces this, advocating population-wide

screening because 1 in 5 people have high Lp(a) and detection is the first step to management (Kronenberg et al., 2022).

In the United States, the 2018 ACC/AHA Guideline on Cholesterol takes a slightly more cautious stance: it lists Lp(a) ≥50 mg/dL (≈125 nmol/L) as a "risk-enhancing factor" that can be used in borderline-risk patients to justify statin therapy (Grundy et al., 2019). It stops short of recommending universal screening, instead suggesting Lp(a) measurement in those with a family history of premature ASCVD or very high LDL unexplained by diet/lifestyle (Grundy et al., 2019). However, awareness of Lp(a) is growing, and the National Lipid Association (NLA) in 2019 advised that it is reasonable to check Lp(a) at least once in adults, especially if there is premature CVD or familial hypercholesterolemia (Wilson et al., 2019). The Canadian Cardiovascular Society 2021 guidelines even integrated Lp(a) into risk assessment, recommending one-time measurement for all and using Lp(a) levels to refine risk category (Pearson et al., 2021). All these guidelines concur that if Lp(a) is elevated, one should ensure optimal control of all other modifiable risk factors (LDL-C, blood pressure, smoking, etc.), since no specific Lp(a)-lowering therapy is yet proven to reduce events (Grundy et al., 2019; Mach et al., 2020). For individuals with very high Lp(a) and ASCVD, guidelines mention consideration of LDL-C targets < 1.4 mmol/L (<55 mg/dL) or even < 1.0 mmol/L in secondary prevention to compensate for the extra risk (Mach et al., 2020). Some European countries (e.g., Germany) have offered lipoprotein apheresis (weekly plasma filtration) for extreme Lp(a) elevation (>60 mg/dL) with progressive ASCVD, and case series indicate this can slow plaque progression (Leebmann et al., 2013). Apheresis is costly and resource-intensive, so it is reserved for select cases (and in some places covered similar to FH patients).

In summary, knowing a patient's Lp(a) level is increasingly considered a standard component of comprehensive risk assessment.

Clinicians should check Lp(a) especially in those with premature or unexplained ASCVD, family history of early events, or in risk discussions where LDL-C alone doesn't fully explain the risk. An elevated Lp(a) can "tip the scales" towards more aggressive therapy of LDL-C (such as adding PCSK9 inhibitor) and other risk factors, as well as inform family screening.

Therapeutic Developments for Lowering Lp(a)

For decades, Lp(a) was considered "undruggable" because lifestyle has minimal effect and conventional lipid drugs have limited impact. However, new therapies are on the horizon. The most advanced are antisense oligonucleotides (ASOs) and small interfering RNA (siRNA) targeting the LPA gene's mRNA. By reducing apo(a) production in the liver, these therapies can dramatically lower Lp(a) levels by up to 80–90% (Tsimikas et al., 2020). One such ASO, pelacarsen (formerly AKCEA-APO(a)-LRx or TQJ230), has completed phase 2 trials showing dose-dependent Lp(a) reduction of ~35–80% with monthly injections (Tsimikas et al., 2020). Pelacarsen is now in an ongoing phase 3 outcomes trial called Lp(a) HORIZON, which is enrolling ~8,000 patients with established CVD and Lp(a) ≥70 mg/dL to test whether lowering Lp(a) will reduce heart attacks, strokes, etc. (NCT04023552). This trial, expected to report results by 2025–2026, is critically important as it will directly answer if targeting Lp(a) improves outcomes. Another agent, an siRNA called olpasiran (AMG 890), has shown >90% Lp(a) reduction in a phase 2 trial (BALLAD) with infrequent dosing (every 12 weeks) (Koren et al., 2022). It is also being moved into a large outcomes trial (planned as the OCEAN(a)-OUTCOMES study). If these trials are positive, we may soon have the first dedicated Lp(a)-lowering drugs, finally enabling us to treat what we currently only can acknowledge as a risk factor.

In the meantime, clinicians managing patients with high Lp(a) should focus on aggressive control of LDL-C (often via PCSK9 inhibitors, which have the side benefit of modest Lp(a) reduction), as well as all other risk factors. Some experts also suggest that aspirin might be particularly beneficial in primary prevention for those with very high Lp(a) (to mitigate thrombosis risk), although this is not formally established and must be balanced against bleeding risk (Bittner et al., 2020). Importantly, patient education is key: individuals with high Lp(a) should understand it is a hereditary factor they have no control over, but that knowing about it allows them to be more proactive with controllable factors. Family screening for Lp(a) is reasonable given the heritability.

In summary, Lp(a) represents a paradigm shift in how we think about cholesterol and CVD risk – it is cholesterol-rich and pro-atherogenic, yet not captured by LDL-C and not modified by diet or routine meds. With Lp(a) now measured more widely and new therapies in development, it stands to become an integral part of personalized CVD prevention in the coming years. Expert cardiologists should keep abreast of this field, as we may soon "go beyond LDL" in practice by specifically targeting Lp(a) in high-risk patients, thereby chipping away at residual risk.

Inflammation and Cardiovascular Disease

The inflammatory hypothesis of atherosclerosis – once a novel idea – is now an established pillar of CVD pathophysiology. Atherosclerosis is not merely a lipid storage disease but a chronic inflammatory condition of the arterial wall, in which risk factors (like hypercholesterolemia, smoking, hypertension, diabetes) incite endothelial dysfunction, immune cell recruitment, and cytokine release that drive plaque formation and instability (Libby, 2021). High-sensitivity C-reactive protein (hs-CRP), a systemic inflammatory biomarker, emerged in the 1990s as a strong

independent predictor of myocardial infarction and stroke (Ridker et al., 1997). Importantly, CRP levels correlate only modestly with LDL-C; thus, they capture a different aspect of risk – often termed "residual inflammatory risk." About 20–40% of statin-treated patients maintain elevated hs-CRP (>2 mg/L) despite achieving low LDL-C, indicating ongoing inflammation that is associated with higher event rates (Ridker et al., 2018). This has raised the critical question: can directly reducing inflammation (without necessarily changing lipid levels) reduce CVD events? Over the past decade, landmark clinical trials have finally answered this question, providing proof-of-concept that inflammation is a treatable driver of CVD.

Inflammation in Atherosclerosis: Pathway Overview

At the lesion level, atherosclerotic plaques develop when apoB-containing lipoproteins (LDL, Lp(a), remnants) infiltrate the intima and provoke an inflammatory response. Monocytes adhere and migrate into the intima, differentiating into macrophages that ingest modified lipoproteins (forming foam cells). These activated macrophages and other immune cells (T-cells, mast cells) secrete pro-inflammatory cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α, which perpetuate a cycle of inflammation and recruit more cells (Hansson & Libby, 2015). The NLRP3 inflammasome is a key intracellular complex in macrophages that, when triggered by stimuli like cholesterol crystals or oxidative stress, leads to activation of caspase-1 and release of IL-1β (Swirski & Nahrendorf, 2018). IL-1β in turn stimulates production of IL-6 and other acute phase reactants including CRP from the liver. Chronic low-grade inflammation contributes to plaque growth and destabilization (thin fibrous caps, more rupture-prone). Furthermore, systemic inflammatory diseases (e.g., rheumatoid arthritis, lupus, psoriasis) are known to accelerate atherosclerosis, underscoring the role of inflammation in CVD

(Libby, 2021). Notably, many risk factors have an inflammatory component: for example, visceral adiposity releases inflammatory cytokines; periodontitis and other chronic infections can raise systemic inflammation and have been linked to CVD risk (Ridker et al., 2019). Given this understanding, it is logical that targeting inflammatory pathways might reduce cardiovascular events. The challenge has been doing so safely and specifically without compromising host defenses or causing undue side effects.

Inflammatory Biomarkers and Risk Stratification

hs-CRP is the most validated inflammatory biomarker in CVD risk prediction. Numerous cohort studies have found that elevated hs-CRP (in, say, the top quartile, >3 mg/L) approximately doubles the risk of future coronary events relative to low hs-CRP (<1 mg/L), independent of LDL-C (Ridker et al., 2002). CRP was incorporated into the Reynolds Risk Score and has been considered as a risk "enhancer" in guidelines (Grundy et al., 2019). The aforementioned JUPITER trial (Ridker et al., 2008) provided compelling clinical evidence: in ~18,000 apparently healthy individuals with LDL <130 mg/dL but hs-CRP ≥2 mg/L, rosuvastatin lowered CRP and LDL and led to a 44% reduction in MI, stroke, or CV death vs placebo. JUPITER highlighted that even "low-LDL" individuals benefited from statin if inflammation was present, implying that CRP identified higher-risk patients who would have been missed by LDL alone. Subsequent analyses showed those who achieved both LDL <70 and hs-CRP <2 on statin had the lowest event rates, whereas those with one but not the other goal had higher risk (Ridker et al., 2009). This dual-goal concept (lower cholesterol *and* lower inflammation) has influenced recent prevention approaches – though formal guidelines still prioritize LDL, they acknowledge CRP can be used to motivate therapy in intermediate-risk cases (Grundy et al., 2019). Other biomarkers like IL-6, soluble ICAM-1, and leukocyte counts also correlate with risk, but are less

often measured clinically. Lp-PLA2 (lipoprotein-associated phospholipase A2) is another marker once touted, but trials of its inhibition did not show benefit, and it's rarely used now (O'Donoghue et al., 2014). Overall, hs-CRP remains the pragmatic option if assessing inflammation in practice.

From a global perspective, certain populations have higher inflammatory burden – for instance, high hs-CRP is common in South Asians due to increased central obesity and metabolic inflammation (Anand et al., 2008). Autoimmune disorders like lupus (more prevalent in certain ethnic groups) markedly raise CVD risk as well. These nuances suggest that addressing inflammation might have particular benefits in such subsets, although direct evidence is limited. What is clear is that chronic inflammation contributes to residual risk in many patients, especially those whose risk is not fully explained by LDL (Ridker et al., 2019).

Clinical Trials Targeting Inflammation

The first successful trial to prove that anti-inflammatory therapy can reduce CVD events was the CANTOS trial (Canakinumab Anti-inflammatory Thrombosis Outcomes Study), reported in 2017. CANTOS enrolled over 10,000 patients with prior MI and hs-CRP ≥2 mg/L despite standard care (including statins) (Ridker et al., 2017). Patients were randomized to canakinumab (a monoclonal antibody against IL-1β) at one of three doses vs placebo, given subcutaneously every 3 months. Canakinumab 150 mg (the dose later chosen) achieved a 35–40% reduction in hs-CRP (and IL-6) without affecting lipids. After ~3.7 years, the canakinumab 150 mg group had a 15% reduction in the primary endpoint (CV death, MI, or stroke) compared to placebo (hazard ratio 0.85, p=0.021) (Ridker et al., 2017). Those who achieved on-treatment hs-CRP <2 mg/L had an even larger ~25% risk reduction, whereas those with little CRP response had no benefit (Ridker et al., 2018). This

gradient underscores that the benefit was indeed tied to inflammation lowering. Canakinumab had no effect on LDL or HDL, so CANTOS was a pure test of inflammation hypothesis – and it succeeded, equating to a risk reduction on par with many LDL-focused therapies. However, canakinumab also led to a higher incidence of fatal infections (an expected consequence of suppressing IL-1β, which is important in host defense), and it is extremely costly (as a drug initially developed for rare autoimmune syndromes). Thus, canakinumab has not been adopted in routine practice for CVD prevention, but CANTOS provided proof-of-concept that targeting a specific immune pathway can reduce ASCVD events independent of lipid changes. It also taught that which pathway is targeted matters greatly; IL-1β was evidently a key node in atherosclerotic inflammation.

In contrast, the NIH-funded CIRT (Cardiovascular Inflammation Reduction Trial) tested a broad immunosuppressant, low-dose methotrexate (used in rheumatoid arthritis), in a similar population (post-MI patients with diabetes or metabolic syndrome) (Ridker et al., 2019). Methotrexate, 15–20 mg weekly, did *not* lower IL-1, IL-6, or CRP levels, and correspondingly, the trial showed no reduction in CV events versus placebo (Ridker et al., 2019). CIRT, reported in 2019, was considered a "failed" trial, but in reality it clarified that not all anti-inflammatory strategies will work – the drug must hit the relevant pathway. Methotrexate's anti-inflammatory action is via adenosine and had no impact on the IL-1/IL-6 axis crucial in atherosclerosis. Moreover, methotrexate caused higher rates of liver enzyme elevation and other side effects, underscoring that untargeted immunosuppression is not a viable approach for CVD (Ridker et al., 2019). The divergent outcomes of CANTOS and CIRT highlight that specific inhibition of the IL-1→IL-6→CRP pathway can mitigate atherosclerosis, whereas off-target immunosuppression cannot.

Perhaps the most intriguing development has been the repurposing of colchicine – a cheap, orally administered anti-inflammatory – for secondary prevention. Colchicine broadly inhibits microtubule polymerization and neutrophil function and has been used for gout and pericarditis for decades. Two major trials have tested low-dose colchicine in coronary disease. The first, COLCOT (Colchicine Cardiovascular Outcomes Trial), enrolled ~4,700 patients within 30 days of a myocardial infarction, randomized to colchicine 0.5 mg daily or placebo on top of standard therapies (Tardif et al., 2019). Over ~2 years, colchicine reduced the composite primary endpoint (CV death, MI, stroke, or urgent hospitalization for angina) by 23% (5.5% vs 7.1%; HR 0.77, p=0.02) (Tardif et al., 2019). This result was driven mainly by fewer myocardial infarctions and strokes. In COLCOT, hs-CRP was measured in only a small subset but showed about a 10% reduction with colchicine (Tardif et al., 2019). A slight increase in non-CV mortality was observed (not statistically significant), and there were more side effects like gastrointestinal upset and a numerically higher risk of pneumonia in the colchicine group (though infection risk was much lower than in CANTOS). The second trial, LoDoCo2 (Low-Dose Colchicine 2), studied ~5,500 patients with chronic stable coronary disease (post-MI or with multivessel CAD) with colchicine 0.5 mg daily vs placebo (Nidorf et al., 2020). After a median ~28 months, the primary CV outcome (CV death, MI, ischemic stroke, or coronary revascularization) was 6.8% in the colchicine group vs 9.6% in placebo, a 31% risk reduction (HR 0.69, $p<0.001$) (Nidorf et al., 2020). This solidified that colchicine confers benefit even in stable patients, not just recent MI. LoDoCo2 similarly saw an increase in pneumonia cases (0.9% vs 0.4%) and a slight excess in non-CV mortality that was not statistically significant but warrants observation (Nidorf et al., 2020). Notably, because colchicine trials did not systematically collect CRP or IL-6 levels, the exact degree of inflammation reduction is not fully documented; however,

mechanistic studies show colchicine likely works by blocking the NLRP3 inflammasome and subsequent IL-1 production in activated macrophages (Martínon, 2020). Thus, it targets the same broad pathway as canakinumab but in a less specific (yet evidently effective) way.

The colchicine story is remarkable because it offers an anti-inflammatory strategy that is inexpensive and relatively well-tolerated. Based on these trials, some clinicians have begun prescribing colchicine 0.5 mg daily as part of secondary prevention for high-risk patients (those with recent ACS or recurrent disease), although guidelines have been cautious. The 2021 ESC Prevention Guidelines gave colchicine a weak recommendation (Class IIb: "may be considered") in secondary prevention (Visseren et al., 2021). The uptake is still limited by concerns about long-term safety, potential drug interactions, and the fact that colchicine is not yet universally accepted as standard care. Ongoing studies and registries will help clarify which subsets benefit most (e.g., perhaps those with higher baseline CRP, though in LoDoCo2 patients were unselected by CRP).

Besides colchicine and canakinumab, other anti-inflammatory approaches are under investigation. One is targeting IL-6 directly, since IL-6 is a key downstream mediator (and CRP driver). A phase 2 trial called RESCUE tested ziltivekimab, a monoclonal antibody against IL-6, in patients with chronic kidney disease (a pro-inflammatory state) and high hs-CRP; it showed profound reductions in CRP (up to ~80%) (Ridker et al., 2021). A large outcomes trial with ziltivekimab in high-CRP patients (ZEUS trial) is being planned. Additionally, clinical trials of therapies like methotrexate in rheumatoid arthritis have shown that patients on effective anti-inflammatory regimens have fewer CV events, indirectly supporting the inflammation hypothesis (Solomon et al., 2020). There is also interest in lifestyle and pharmacologic

interventions that reduce inflammation more broadly: for example, aggressive risk factor control (LDL, blood pressure, weight loss) itself can lower inflammation; some GLP-1 agonists and SGLT2 inhibitors for diabetes have been noted to reduce CRP modestly alongside other benefits (Dahl et al., 2021).

One should mention that not all inflammation is equal – the CANTOS vs CIRT dichotomy suggests specific targeting of innate immune pathways relevant to atherosclerosis (like IL-1β) is crucial. General immune suppression or targeting other pathways (like TNF-α in trials with RA patients without success in CAD) has not translated to benefit (Libby, 2021). This means future drug development is focusing on precision anti-inflammatory therapy – damping the atherosclerotic inflammation while minimizing effect on host defense. Colchicine, interestingly, might do this by preferentially affecting neutrophils and the NLRP3 pathway, which is central to plaque inflammation, while having less impact on systemic immunity than expected (its infection signal was mild). Still, vigilance is needed regarding infections if using any chronic anti-inflammatory in CVD patients.

Integration of Inflammation into Clinical Practice

The advent of outcome-proven anti-inflammatories is reshaping preventive cardiology. For patients with known ASCVD, especially if they have residual inflammatory risk (say, hs-CRP >2 mg/L) despite standard therapies, one might consider adding an anti-inflammatory agent. As of 2025, colchicine 0.5 mg daily has the most practical evidence for use – it's included in some guidelines as an option for secondary prevention (Visseren et al., 2021). On the other hand, canakinumab is not used due to cost and safety, and methotrexate is ineffective for CVD. Lifestyle measures that reduce inflammation (dietary changes like Mediterranean diet, regular exercise, smoking cessation) should be emphasized as they have

many benefits including CRP reduction (Bonaccio et al., 2017). In risk assessment, an elevated hs-CRP can tip the scale toward more aggressive intervention – for example, the 2018 ACC/AHA guidelines note hs-CRP ≥2 mg/L (if measured) can favor statin use in borderline risk cases (Grundy et al., 2019).

Still, routine measurement of CRP in all patients is debated. It's readily available and inexpensive, but some argue it doesn't change management if one is already inclined to treat risk factors. Others counter that it identifies high-risk individuals who might otherwise appear intermediate-risk by traditional scores, as in JUPITER. For cardiologists, it is reasonable to measure hs-CRP in patients with premature or recurrent events despite risk factor control, to see if inflammation might be contributing and if they might be candidates for adjunctive therapy like colchicine or (in the future) IL-6 inhibitors. In patients with chronic inflammatory diseases (RA, HIV, psoriasis), one must be mindful that their basal risk is higher and manage risk factors aggressively; some guidelines consider these conditions as risk enhancers or equivalent to one risk-strata higher (Grundy et al., 2019).

The field of "cardio-immunology" is now rapidly evolving. Ongoing trials like Lp(a) HORIZON will intersect with inflammation (since Lp(a) carries oxidized phospholipids that incite inflammation, lowering Lp(a) might have anti-inflammatory effects too). Another area of interest is vaccination – e.g., a vaccine against IL-1 or against certain periodontal bacteria – but that's more speculative at present.

In summary, inflammation is both a marker and mediator of residual cardiovascular risk. We now have evidence-based tools to gauge it (hs-CRP) and to combat it (colchicine, and possibly diet or novel drugs). Integrating inflammation into CVD prevention means we adopt a more holistic view: beyond lipid numbers and blood pressure readings, we consider the immune state of our patients. The

payoff of this approach is potentially large – CANTOS and colchicine trials suggest we can achieve an additional ~15–30% risk reduction on top of standard therapy in selected patients. This could translate into many prevented heart attacks and strokes, especially in those who, despite LDL <70 mg/dL, still have a smoldering inflammatory drive of their atherosclerosis.

Future Directions and Conclusion

As we look beyond LDL-centric prevention, it's evident that residual risk is multifactorial. Triglyceride-rich lipoproteins, Lp(a), and inflammation represent three critical domains where ongoing research and new therapies promise to further reduce ASCVD burden. Future prevention strategies will likely adopt a more personalized approach: for instance, a patient with metabolic syndrome and high triglycerides may benefit from an APA – an apoC-III inhibitor or icosapent ethyl to target remnants – whereas another patient with premature ASCVD and very high Lp(a) might receive an LPA silencing therapy to remove that risk driver. A third patient with persistently high CRP after an MI might be treated with colchicine or an IL-6 inhibitor to quell arterial inflammation.

Clinical guidelines are gradually evolving toward this multifaceted prevention model. One can envision a not-so-distant future "polypill" concept that not only includes an LDL-lowering drug, but also an anti-inflammatory and perhaps an Lp(a)-targeting agent for those who need it. However, achieving this safely will require careful patient selection and monitoring, given potential risks like infection or unknown long-term effects of new agents.

It will be important as well to address global and regional health disparities in these risk factors. Populations vary in prevalence of high Lp(a) and metabolic dyslipidemia; thus, public health strategies might differ – for example, screening for Lp(a) might be especially beneficial in South Asian or African communities where

its prevalence and impact are high. Similarly, combating obesity and diabetes (to reduce triglyceride-rich lipoproteins and inflammation) remains paramount worldwide. Lifestyle remains the cornerstone: diet, exercise, and weight management favorably influence all these factors (except Lp(a) which is genetic) and should never be neglected in the rush to novel drugs.

In conclusion, the era of focusing solely on LDL-C is over. LDL reduction has taken us a long way, but not far enough to eliminate cardiovascular disease. By shifting attention "beyond LDL" to triglycerides, Lp(a), and inflammation, we target the residual risk that has been plaguing our patients despite otherwise optimal therapy. High-quality evidence from genetics, epidemiology, and clinical trials now validates each of these factors as legitimate therapeutic targets. For expert cardiologists, staying abreast of these developments is essential: it means knowing when to check an Lp(a) level, how to interpret and address an elevated CRP, and how to apply trial data on therapies like icosapent ethyl or colchicine. It also means contributing to and awaiting the results of ongoing landmark trials (e.g., Lp(a)-lowering therapies, IL-6 inhibitors), which could open new chapters in prevention. Ultimately, a comprehensive approach that integrates lipid management with inflammation control and genetic risk factor mitigation holds the promise of truly curbing the global ASCVD epidemic. By going beyond LDL, we move closer to the goal of maximal cardiovascular risk reduction, tailoring prevention to the full spectrum of pathobiology underlying atherosclerosis.

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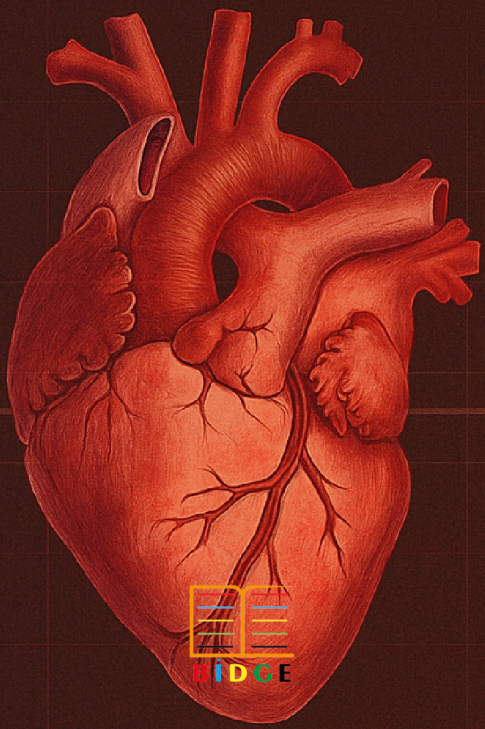
KARDİYOLOJİDE YENİ YAKLAŞIMLAR

SPOR, MİKROBİYOTA, BİYOBELİRTEÇLER ve LDL DIŞI RİSKLERLE DEĞİŞEN KLİNİK PRATİK



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