EVALUACIÓN DE LALESIÓN MIOCÁRDICA PERIOPERATORIA EN CIRUGÍA NO CARDÍACA CON TROPONINA T CARDÍACA DE ALTA SENSIBILIDAD E IMAGEN CARDÍACA AVANZADA RESULTADOS Y COSTE-EFECTIVIDAD DE SU EVALUACIÓN SISTEMÁTICA

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Programa de Doctorado en Metodología de la Investigación Biomédica y Salud Pública

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Evaluación de la lesión miocárdica perioperatoria en cirugía no cardiaca con Troponina T cardiaca de alta sensibilidad e imagen cardíaca avanzada

Resultados y coste-efectividad de su evaluación sistemática

Tesis doctoral: Ekaterine Popova Sherozia

Marzo de 2024

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"Cuando has eliminado lo imposible, lo que quede, por improbable que sea, debe ser la verdad" - Arthur Conan Doyle (Sherlock Holmes).

"Una onza de prevención vale más que una libra de cura" - Benjamin Franklin.

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Resumen

Antecedentes

Anualmente, se realizan unos 300 millones de procedimientos quirúrgicos en todo el mundo. Avances en las técnicas anestésicas y quirúrgicas permiten intervenir a pacientes de mayor edad y con comorbilidades; son pacientes con alto riesgo de complicaciones. La lesión miocárdica perioperatoria (LMP) en cirugía no cardíaca es una complicación asociada a una mayor mortalidad a corto y largo plazo. Sin un cribado sistemático con troponina cardíaca (Tnc), especialmente medida con métodos de alta sensibilidad, un número significativo de LMP pueden pasar clínicamente desapercibidas. No obstante, la evidencia sobre los programas de cribado de esta condición es limitada, no se ha analizado convenientemente su coste-efectividad y hay pocos estudios que hayan evaluado la fisiopatología de la LMP.

Objetivos

Los objetivos de la presente tesis fueron: 1) Evaluar la implementación del cribado sistemático con TncT de alta sensibilidad (TncT-as), registrando la incidencia de LMP, mortalidad y complicaciones cardiovasculares mayores (CCVM) asociadas, 2) Evaluar la relación de coste-efectividad del cribado sistemático, comparándolo con la práctica clínica habitual y, 3) Evaluar la utilidad de las pruebas avanzadas de imagen cardiaca, como la tomografía computarizada cardiaca (TCC) y la resonancia magnética cardiaca (RMC), para generar conocimiento sobre la(s) etiología(s) de la LMP.

Métodos

La tesis incluye tres estudios originales que han sido realizados con distintas perspectivas metodológicas y han sido publicados en revistas biomédicas indexadas y revisadas por pares.

El Estudio I consistió en un estudio de cohorte, prospectiva y observacional realizado en un único hospital terciario y universitario español. Se incluyeron pacientes con elevado riesgo cardiovascular (CV), intervenidos de cirugía mayor no cardíaca que requirió al menos una noche de ingreso. En todos los pacientes se midió la TncT-as preoperatoriamente y a las 48 y 72h tras la cirugía. La LMP se definió con un valor postoperatorio de TncT-as ≥14 ng/L, con un aumento mínimo del ≥50% sobre el valor previo a la cirugía. Los pacientes con LMP recibieron una evaluación cardiológica y tanto en ellos como en aquellos sin LMP se realizó un seguimiento a los 30 días y un año después de la cirugía. Se registraron la mortalidad y las CCVM.

El estudio II a partir de la misma cohorte de pacientes que el Estudio I, evaluó el coste-efectividad del cribado sistemático de la LMP con TncT-as comparándolo con la atención clínica habitual (sin cribado) mediante el cálculo, entre otros parámetros, de la relación coste-efectividad incremental (*Incremental Cost-Effectiveness Ratio - ICER*) y la estimación de la disposición a pagar (*WTP-Willingness to pay*), por cada caso adicional de LMP detectada.

El estudio III consistió en un estudio piloto caso-control en pacientes con LMP (casos) y sin LMP (controles). Se incluyeron pacientes del estudio I y pacientes provenientes de otro hospital universitario, terciario; todos ellos intervenidos de cirugía mayor no cardiaca. Tanto a los casos como a los controles se les realizó una TCC y una RMC durante el primer mes tras el alta hospitalaria con el objetivo de identificar las etiologías de la LMP.

Resultados

El estudio I incluyó a 1477 pacientes con un seguimiento completo al mes y al año de la cirugía. El cribado sistemático de la LMP fue desarrollado por un equipo multidisciplinario que identificó los desafíos y complejidades existentes para lograr una implementación óptima. La incidencia de LMP fue del 15,7%, los pacientes con LMP presentaron más frecuentemente antecedentes CV, concentraciones preoperatorias más elevadas de TncT-as, así como más alteraciones hemodinámicas, sangrado o trastornos del ritmo cardíaco perioperatorios. En los pacientes con LMP la tasa de mortalidad por cualquier causa fue del 1,7% en el primer mes y aumentó al 11,2% al año; la mortalidad CV también aumentó de 0,9 a 3,9%. La incidencia de CCVM fue del 9,5% y del 8,6% al mes y al año, respectivamente.

En el estudio II, que analizó la misma cohorte de 1477 pacientes, la estrategia de cribado sistemático con TncT-as permitió detectar 10 veces más casos de LMP (15,7% vs. 1,6%) que la estrategia de práctica clínica habitual; se detectaron 208 LMP adicionales. El ICER fue de 425 euros (€) por un caso de LMP detectado adicionalmente, con una disposición a pagar más que razonable para conseguir el 100% de iteraciones coste-efectivas.

El estudio III, que fue un estudio piloto, incluyó a 52 pacientes con LMP y 12 controles. Mediante TCC se observó que la existencia de enfermedad arterial coronaria (EAC) significativa no difería entre casos con LMP y controles (30% vs 33%, respectivamente). Sin embargo, mediante RMC patrones y segmentos cardio-isquémicos se observaron únicamente en los pacientes con LMP.

Conclusiones

La implementación del cribado sistemático con TncT-as de la LMP en pacientes de alto riesgo intervenidos de cirugías no cardíacas, permite detectar esta lesión en una elevada proporción de pacientes. La implementación del cribado es viable y coste-efectiva en un horizonte temporal de 30 días; pero su introducción en la rutina clínica no está exenta de dificultades. La LMP se asocia a una elevada morbimortalidad a corto y largo plazo y la isquemia cardíaca puede ser causada por mecanismos no aterotrombóticos. Los datos obtenidos avalan la necesidad de adoptar el cribado de la LMP en esta población de alto riesgo en la práctica clínica.

Resum

Antecedents

Anualment es realitzen uns 300 milions de procediments quirúrgics a tot el món. Avanços en les tècniques anestèsiques i quirúrgiques permeten intervenir pacients de major edat i amb comorbiditats; són pacients amb alt risc de complicacions. La lesió miocàrdica perioperatòria (LMP) en cirurgia no cardíaca és una complicació associada a una major mortalitat a curt i llarg termini. Sense un cribratge sistemàtic amb troponina cardíaca (Tnc), especialment mesurada amb mètodes d'alta sensibilitat, un nombre significatiu de LMP poden passar clínicament desapercebudes. No obstant d'això, l'evidència sobre els programes de cribratge d'aquesta condició és limitada, el cost-efectivitat del mateix no ha estat convenientment analitzat, i hi ha pocs estudis que hagin avaluat la fisiopatologia de la LMP.

Objectius

Els objectius de la present tesi van ser: 1) Avaluar la implementació del cribratge sistemàtic amb TncT d'alta sensibilitat (TncT-as), registrant la incidència de LMP, mortalitat i complicacions cardiovasculars majors (CCVM), 2) Avaluar la relació del cost -efectivitat d'aquest cribratge, comparant-ho amb la pràctica clínica habitual i, 3) Avaluar la utilitat de les proves avançades d'imatge cardíaca, com la tomografia computeritzada cardíaca (TCC) i la ressonància magnètica cardíaca (RMC), per generar coneixement sobre l'etiologia(es) de la LMP.

Mètodes

La tesi inclou tres estudis originals que han estat realitzats amb diferents perspectives metodològiques i han estat publicades a revistes biomèdiques indexades i revisades per parells.

L'Estudi I va consistir un estudi de cohort, prospectiu i observacional realitzat a un únic hospital terciari i universitari espanyol, on van incloure pacients amb risc cardiovascular (CV) elevat, intervinguts de cirurgia major no cardíaca que va requerir almenys una nit d'ingrés. En tots els pacients es va mesurar la TncT-as abans de la cirurgia i a les 48 i 72 h després de cirurgia. La LMP es va definir com un valor postoperatori de TncT-as ≥14 ng/L, amb un augment mínim del ≥50% sobre el valor preoperatori. Els pacients amb LMP van rebre una avaluació cariològica i tant en ells com en aquells sense LMP es va fer

L'estudi II a partir de la mateixa cohort de pacients que l'Estudi I, va avaluar el cost-efectivitat del cribratge sistemàtic de la LMP amb TncT-as comparant-lo amb l'atenció clínica habitual (sense cribratge) mitjançant el càlcul, entre altres paràmetres, de la relació cost-efectivitat incremental (*Incremental Cost-Effectiveness Ratio - ICER*) i la estimació de la disposició a pagar (*WTP-Willingness to pay*), per cada cas addicional de LMP detectada.

L'estudi III va consistir un estudi, pilot de cas-control en pacients amb LMP (casos) i sense LMP (controls). S'hi van incloure pacients de l'estudi I, així com pacients provinents de un altre hospital universitari, terciari; tots ells intervinguts de cirurgia major no cardíaca. Tant als casos com als controls se'ls va fer una TCC i una RMC durant el primer mes després de l'alta hospitalària per identificar les etiologies de la LMP.

Resultats

L'estudi I va incloure 1.477 pacients amb un seguiment complet al mes i a l'any de la cirurgia. El cribratge sistemàtic de la LMP va ser desenvolupat per un equip multidisciplinari que va identificar els desafiaments i complexitats existents per aconseguir una implementació òptima. La incidència de LMP va ser del 15,7%, els pacients amb LMP van presentar més freqüentment antecedents CV, concentracions preoperatòries més elevades de TncT-as -comparades amb els pacients que no van desenvolupar LMP- així com més alteracions hemodinàmiques, sagnat o trastorns del ritme cardíac perioperatoris. Als pacients amb LMP la taxa de mortalitat per qualsevol causa va ser de l'1,7% el primer mes i va augmentar a l'11,2% a l'any; la mortalitat CV també va augmentar de 0,9 a 3,9%. La incidència de CCVM va ser del 9,5% i el 8,6% al mes i a l'any, respectivament.

En l'estudi II, que va analitzar la mateixa cohort de 1477 pacients, l'estratègia de cribratge sistemàtic amb TncT-as va permetre detectar 10 vegades més casos de LMP (15,7% vs. 1,6%) que l'estratègia de pràctica clínica habitual; es van detectar 208 LMP addicionals. El ICER va ser de 425 euros (€) per un cas de LMP detectat addicionalment, amb una disposició a pagar més que raonable per aconseguir el 100% d'iteracions cost-efectives.

L'estudi III, que va ser un estudi, pilot, va incloure 52 pacients amb LMP i 12 controls. Mitjançant TCC es va observar que la existència de malaltia arterial coronària (EAC) significativa no diferia entre casos amb LMP i controls (30% vs. 33%, respectivament). No obstant això, mitjançant RMC patrons i segments càrdio-isquèmics es van observar únicament en els pacients amb LMP.

Conclusions

La implementació del cribratge sistemàtic amb TncT-as de la LMP en pacients d'alt risc intervinguts de cirurgies no cardíaques permet detectar aquesta lesió en una proporció elevada de pacients. La implementació del cribratge és viable i cost-efectiva en un horitzó temporal de 30 dies; però la seva introducció a la rutina clínica no està exempta de dificultats. La LMP s'associa a elevada morbimortalitat a curt i llarg termini i la isquèmia cardíaca pot ser causada per mecanismes no aterotrombòtics. Les dades obtingudes avalen la necessitat d'adoptar el cribratge de la LMP en aquesta població de alt risc a la pràctica clínica.

Abstract

Background

About 300 million surgical procedures are performed annually worldwide. Advances in anesthetic and surgical techniques allow the intervention of older patients and patients with comorbidities; They are patients at elevated risk of complications. Perioperative myocardial injury (PMI) in non-cardiac surgery is common complication associated with major short- and long-term mortality. Without systematic screening with cardiac troponin (cTn), especially measured with high-sensitive methods, a considerable number of PMI may go clinically undetected. However, the evidence on screening programs for this condition is limited, its cost-effectiveness has not been adequately, and there are few studies that have evaluated the pathophysiology of PMI.

Objectives

The objectives of this thesis were: 1) To evaluate the implementation of systematic screening with high-sensitivity cardiac troponin T (hs-cTnT), recording the incidence of PMI, mortality and major cardiovascular complications (MACE), 2) To evaluate the cost-effectiveness of this screening, comparing it with usual clinical practice and, 3) To evaluate the usefulness of advanced cardiac imaging tests, such as cardiac computed tomography angiography (CCTA) and magnetic resonance imaging (MRI), to generate knowledge about the etiology(s) of PMI.

Methods

The thesis includes three original studies that have been conducted with different methodological perspectives and have been published in peer-reviewed, indexed biomedical journals.

Study I consisted of prospective, observational cohort study conducted in a single Spanish tertiary and university hospital. Patients with high cardiovascular (CV) risk, undergoing major non-cardiac surgery that required at least one night of hospitalization, were included. In all patients, hs-cTnT was measured preoperatively and 48 and 72 hours after surgery. PMI was defined as a postoperative hs-cTnT value ≥14 ng/L, with a minimum ≥50% increase over the preoperative value. Patients with PMI received a cardiological evaluation and all patients (with and without PMI) were followed up 30 days and one year after surgery. Mortality and MACE were recorded.

Study II, based on the same cohort of patients as Study I, evaluated the cost-effectiveness of systematic PMI screening with hs-cTnT, comparing it with usual clinical care (without screening) by calculating, among other parameters, of the incremental cost-effectiveness ratio (ICER) and the estimate of willingness to pay (WTP-Willingness to pay), for each additional case of detected PMI.

Study III consisted of pilot case-control study in patients with PMI (cases) and without PMI (controls). Patients from study I, as well as patients from another tertiary university hospital were included; all of them underwent major non-cardiac surgery. Both cases and controls underwent CCTA and MRI during the first month after hospital discharge with the aim of identifying the etiologies of PMI.

Results

Study I included 1477 patients with complete follow-up one month and one year after surgery. Systematic PMI screening was developed by a multidisciplinary team that identified existing challenges and complexities for optimal implementation. The incidence of PMI was 15.7%; patients with PMI had more frequently a CV history, higher preoperative hs-cTnT concentrations, and more hemodynamic alterations, bleeding, or perioperative heart rhythm disorders. In patients with PMI the all-cause mortality rate was 1.7% in the first month and increased to 11.2% at one year; CV mortality also increased from 0.9 to 3.9%. The incidence of MACE was 9.5% and 8.6% at one month and one year, respectively.

In study II, from the same cohort of 1477 patients. The systematic screening strategy with hs-cTnT detected ten times more cases of PMI (15.7% vs. 1.6%) than the usual clinical practice strategy; 208 additional PMI cases were detected. The ICER was 425 euros (€) for each of the additionally detected PMI, with more than reasonable WTP to achieve 100% of cost-effective iterations.

Study III, which was a pilot study, included 52 patients with PMI and 12 controls. By CCTA was observed that the existence of significant coronary artery disease (CAD) did not differ between cases with PMI and controls (30% vs 33%, respectively). However, by MRI cardio-ischemic patterns and segments were only observed in patients with PMI.

Conclusions

The implementation of systematic screening with hs-cTnT for PMI in high-risk patients undergoing non-cardiac surgeries allows to detect this injury in a high proportion of patients. The implementation of screening is feasible and cost-effective in a time horizon of 30 days; but its introduction into clinical routine is not exempt of difficulties. PMI is associated with high short- and long-term morbidity and mortality and cardiac ischemia can be caused by non-atherothrombotic mechanisms. The data obtained support the need to adopt PMI screening in this high-risk population in clinical practice.

LISTADO DE ABREVIATURAS

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CCVM - Complicaciones Cardio Vasculares Mayores

CV - Cardiovascular

IM - Infarto de Miocardio

LMP - Lesión Miocárdica Perioperatoria

ICC - Insuficiencia Cardíaca Congestiva

Tnc - Troponina cardiaca

ECG - Electrocardiograma

TncT-as - Troponina cardiaca T medida con métodos de alta sensibilidad

EAC - Enfermedad Arterial Coronaria

AVC - Accidente Vascular Cerebral

FA - Fibrilación Auricular

TncI - Troponina cardiaca I

BNP *(Brain Natriuretic Peptide)* - Péptido natriurético de tipo B

NT-proBNP - Fragmento aminoterminal del propéptido natriurético de tipo B

OMS - Organización Mundial de la Salud

FGe - Filtración Glomerular estimada

ICER *(Incremental Cost-Effectiveness Ratio)* - Relación (ratio) de coste-efectividad incremental

QALY *(Quality-Adjusted Life Year)* - Año de vida ajustado por calidad

EP - Embolia Pulmonar

TCC - Tomografía Computarizada Cardiaca

RMC - Resonancia Magnética Cardiaca

IRCR - Índice de Riesgo Cardiaco Revisado

AIT - Accidente Isquémico Transitorio

IECA - Inhibidores De La Enzima Convertidora De Angiotensina

LISTADO DE ABREVIATURAS

CEAC *(Cost-Effectiveness Acceptability Curve)* - Curva de Aceptabilidad de Coste-Efectividad

WTP *(Willingness to pay)* - La Disposición a Pagar

CAD-RADS *(Coronary Artery Disease - Reporting and Data System)* - Sistema de Informes y Datos de Enfermedad de las Arterias Coronaria

1. INTRODUCCIÓN

1. INTRODUCCIÓN

1.1. Preámbulo. Medicina Perioperatoria

La medicina perioperatoria es una subespecialidad que ha nacido impulsada por la aplicación de técnicas quirúrgicas y anestésicas avanzadas en pacientes con estados de salud cada vez más complejos. Su ámbito temporal de actuación no está acotado, pero se entiende que abarca desde el momento en que se indica una cirugía hasta la completa recuperación del paciente. La medicina perioperatoria, al abordar una variedad de procesos interrelacionados, es multidisciplinaria y está centrada en el paciente, con el objetivo principal de mejorar los resultados de todos los procesos involucrados y disminuir las complicaciones asociadas con la cirugía. Este objetivo requiere, por lo tanto, la evaluación preoperatoria con la cuantificación de los riesgos del procedimiento específico para cada paciente, la planificación de la intervención - colaborativa con el paciente-, la optimización preoperatoria de las comorbilidades si las hubiera, la estandarización de los cuidados durante y después del procedimiento quirúrgico, atendiendo a la mejor evidencia científica disponible, y la planificación al alta hospitalaria. También podría incluirse como objetivo la colaboración con los equipos de atención primaria para el proceso de recuperación en el ámbito extrahospitalario.

Posiblemente, las iniciativas de investigación más representativas en este tema han sido los programas multimodales de prehabilitación y los conocidos como ERAS (*Enhance Recovery After Surgery*) centrados en la recuperación postoperatoria. Estos trabajos han sugerido que aún existen aspectos del proceso quirúrgico susceptibles de optimización, que, eventualmente, permitirían mejorar los resultados clínicos y la eficiencia de la atención perioperatoria. Adicionalmente, la creciente presión para contener los costes sanitarios, el envejecimiento progresivo de la población que incrementa su riesgo quirúrgico, así como la rápida y creciente incorporación de nuevas tecnologías sanitarias a la práctica médica habitual, entre otros factores, requieren de una continua evaluación y adaptación de los procesos de la atención médica perioperatoria, lo que genera nuevas necesidades y oportunidades para seguir investigando.

1.2. Cirugía y complicaciones cardiovasculares. Epidemiología

Los procedimientos quirúrgicos representan un estrés considerable para los pacientes intervenidos debido a la agresividad de los procedimientos quirúrgicos y anestésicos - incluyendo la intubación y extubación, el dolor asociado a la cirugía practicada u otras circunstancias como la hipotermia o el sangrado. El número de intervenciones quirúrgicas realizadas en el mundo ha aumentado exponencialmente, superando en la actualidad los 300 millones de casos anuales, lo que supone una intervención quirúrgica por cada 25 habitantes/año (1); aunque en los países desarrollados, la tasa es incluso mayor, llegando a una intervención por cada 10 habitantes/año (2). Aproximadamente, el 85%

de estos procedimientos quirúrgicos no son cardíacos (3) y más de 100 millones de estos se realizan en pacientes mayores de 45 años (2,4). En España, el informe de Instituto Nacional de Gestión Sanitaria (INGESA) reporta más de cinco millones de intervenciones quirúrgicas anuales, de las que aproximadamente un tercio precisan ingreso hospitalario durante al menos 24 horas.

Aunque la cirugía posee un gran potencial curativo y contribuye significativamente al bienestar de los pacientes, y a pesar de los importantes avances en técnicas quirúrgicas y anestesia dirigidos a minimizar el estrés quirúrgico, las complicaciones cardiovasculares mayores (CCVM) perioperatorias siguen siendo la segunda complicación más frecuente en la población quirúrgica, inmediatamente después de las complicaciones infecciosas (5). Estas CCVM perioperatorias no sólo prolongan la duración de la estancia hospitalaria y la necesidad de cuidados postquirúrgicos, sino que también incrementan el riesgo de mortalidad (6).

En un reciente estudio de cohortes que incluyó a 40 000 pacientes mayores de 45 años, sometidos a cirugía no cardiaca, las tres complicaciones más frecuentemente asociadas con la mortalidad fueron la hemorragia grave (15,6%), la lesión miocárdica (13%) y la sepsis (12%) (7). Por lo tanto, la mortalidad perioperatoria ya representa un problema de salud que, en el futuro próximo, no hará más que aumentar, dado que actualmente ni la edad avanzada ni la existencia de comorbilidades previas se consideran factores excluyentes para la cirugía, excepto en casos muy específicos (8).

Se estima que la mortalidad perioperatoria representa casi el 8% de la mortalidad total a nivel mundial, siendo la tercera causa más común de muerte en el mundo, superada únicamente por las muertes por enfermedades cardíacas isquémicas y los accidentes cerebrovasculares (1) **(Figura 1).**

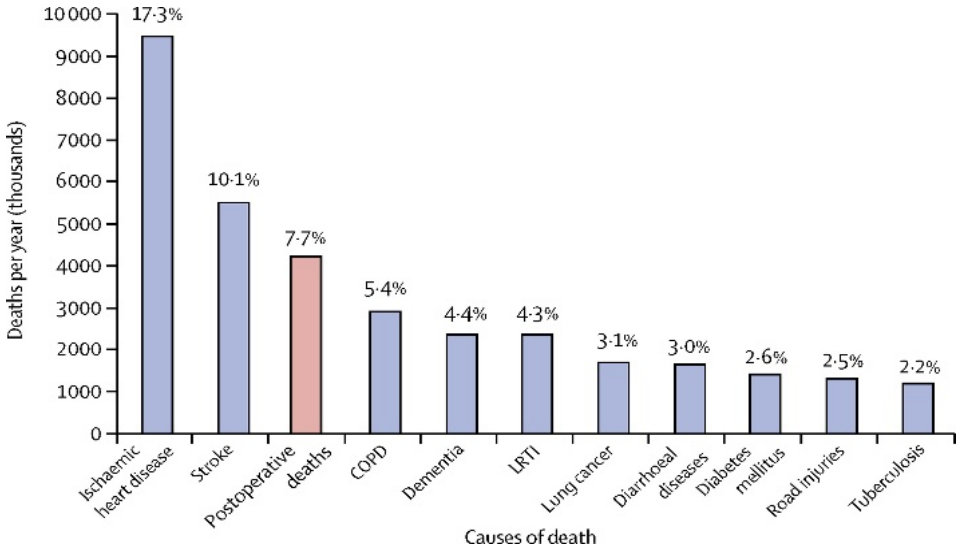

Figura 1. Mortalidad mundial. Causas más frecuentes.
Fuente: *Lancet. 2019; 393(10170):401. doi:10.1016/S0140-6736(18)33139-8.*

El estudio de cohortes VISION (9) que incluyó a 15 133 pacientes de edad ≥45 años, intervenidos de cirugía no cardíaca y que requirieron, al menos, de una noche de hospitalización, fue el primero en demostrar que existía una mortalidad por causa cardiovascular (CV) del 1,90 % (IC 95% 1,7-2,1%) a los 30 días de la intervención que era independiente del riesgo CV prequirúrgico del paciente.

En Europa, el *European Surgical Outcomes Study* (Eusos), a partir de datos obtenidos en 50 000 pacientes adultos sometidos a cirugía no cardíaca con ingreso en hospitales europeos, reportó una mortalidad del 4% en los primeros 60 días de postoperatorio (10).

1.3. Daño miocárdico en cirugía no cardíaca

El infarto de miocardio (IM) tras cirugía no cardiaca es una CCVM frecuente que se asocia con complicaciones severas. Uno de los primeros estudios sobre las CCVM en cirugía no cardíaca fue el estudio POISE (*PeriOperative ISchemic Evaluation*) (11), un ensayo clínico controlado y aleatorizado que incluyó a 8351 pacientes y evaluó el efecto del tratamiento con betabloqueante (Metropolol) frente a placebo sobre el riesgo de CCVM, concretamente la muerte de causa CV, IM no fatal y paro cardíaco no fatal. El estudio demostró que, en pacientes de 45 años o más, intervenidos de una cirugía no cardíaca que requería al menos de una noche de ingreso hospitalario y que presentaban enfermedades cardíacas conocidas, riesgo de padecerlas o factores CV, el 6,9% de los pacientes del grupo placebo presentaron las CCVM perioperatorias evaluadas, siendo el IM perioperatorio (5,1%) la complicación más frecuentemente observada. La mortalidad por causas CV fue del 1,4% en los 30 días siguientes a la cirugía.

El concepto de “lesión miocárdica perioperatoria (LMP)” es relativamente reciente. Se refiere al daño miocárdico producido después de la cirugía no cardíaca que no cumple con los criterios de la definición universal del IM (12). Por su asociación con las morbilidades y la mortalidad a corto (un mes) y a más largo plazo (un año) de la intervención quirúrgica (6), la LMP se considera una de las CCVM más comunes en el contexto de la cirugía no cardiaca y por ello, ha ido ganando relevancia clínica en los últimos años (13).

Más del 80% de las LMP se presentan sin síntomas o signos evidentes, por lo que pasan desapercibidas (14). Se estima que la mayoría de las LMP ocurren durante las primeras 48 horas postcirugía (15). Este período coincide con el uso extensivo de la sedación y la analgesia para el control del dolor postoperatorio, y los síntomas de la isquemia miocárdica, como el dolor torácico, pueden quedar enmascarados (14-16). Otro factor que dificulta la detección temprana de LMP es la atribución de los signos/síntomas clínicos sugestivos de la misma a condiciones alternativas que se presentan frecuentemente en el período postoperatorio como pueden ser trastornos del ritmo cardíaco,

hipotensión, hipovolemia, anemia (todas ellas reconocidas causas de LMP) o náuseas y vómitos. Además, algunos de estos signos y síntomas pueden coincidir con los efectos secundarios al uso de anestésicos volátiles y opioides y no a sus potenciales causas cardíacas (17). De manera similar, signos precoces de insuficiencia cardíaca congestiva (ICC) también pueden interpretarse como causados por una sobrecarga de volumen debida a la administración perioperatoria de líquidos endovenosos. La forma de presentación de la LMP, predominantemente subclínica o con clínica inespecífica, dificulta su óptima detección en la práctica clínica habitual, lo que a su vez puede retrasar su diagnóstico. La falta de diagnóstico de la LMP o su retraso es un problema sanitario relevante ya que la mortalidad de la LMP asintomática es equiparable a la mortalidad asociada con el IM perioperatorio (13-16).

1.3.1. Definición de lesión miocárdica perioperatoria (LMP)

A diferencia del IM, no existe un consenso universal sobre la definición diagnóstica de la LMP. Probablemente, ello es debido a que actualmente coexisten diferentes definiciones que utilizan diferentes concentraciones y seriación temporal de los biomarcadores cardíacos - fundamentalmente troponina cardíaca medida con métodos de alta sensibilidad- empleados para su detección.

Existen dos grupos de investigación que han desarrollado los principales estudios multicéntricos sobre la LMP, a partir de los cuáles se han propuesto la denominación de esta condición y sus criterios diagnósticos. Uno de los grupos, canadiense, ha promovido los estudios VISION y POISE que han incluido pacientes de Norte y Sudamérica, Asia, Europa, África y Australia. Para denominar a la LMP, este grupo ha propuesto el término "*Myocardial Injury after Noncardiac Surgery*", abreviado como MINS (15-16). El otro grupo, autores del estudio BASEL-PMI, que exclusivamente ha incluido a pacientes helvéticos, ha propuesto denominar a la LMP como "*Perioperative Miocardial Injury*", abreviada como PMI (13).

Independientemente de las diferentes denominaciones, los dos grupos mencionados coinciden en que las concentraciones de troponina cardiaca (Tnc), especialmente si se mide con métodos de alta sensibilidad, es la base del diagnóstico de la LMP. No obstante, ambos grupos difieren en alguno de sus enfoques diagnósticos.

El grupo canadiense del estudio VISION midió la TncT exclusivamente después de la cirugía, utilizando como criterio para diagnosticar MINS la existencia de cualquier elevación postoperatoria de la misma producida por isquemia cardíaca que ocurriera durante los 30 días posteriores de la cirugía, con o sin síntomas adicionales o cambios en el electrocardiograma (ECG) (15-16). Por su parte, en el estudio BASEL-PMI, desarrollado entre los años 2014 y 2015, se midió la troponina cardiaca T con un método de alta sensibilidad (TncT-as) antes y después de la cirugía, lo que no solo permitía la detección de elevaciones postoperatorias de TncT-as, sino también la evaluación de su evolución dinámica desde el

período pre- hasta el postoperatorio. Este enfoque distinguía las elevaciones agudas de Tnc de las crónicas. El estudio BASEL-PMI se realizó en pacientes considerados “de alto riesgo”, definición que incluyó a mayores de 65 años o aquellos menores de esta edad con antecedentes de enfermedad arterial coronaria (EAC) o arterial periférica o accidente vascular cerebral (AVC). El estudio no excluyó las causas secundarias de aumento de las concentraciones de TncT-as como la existencia de fibrilación auricular (FA) o ICC previa a la intervención y el diagnóstico de PMI se basó en el aumento absoluto de TncT-as igual o mayor a 14 ng/L (límite superior de referencia en población sana), independientemente del valor máximo de las mediciones postoperatorias (13).

1.3.2. Detección de LMP; biomarcadores cardiacos

Los biomarcadores cardíacos se utilizan en las diferentes etapas de los procedimientos quirúrgicos con diferentes objetivos. En primer lugar, las concentraciones elevadas de biomarcadores identifican a los pacientes con un alto riesgo de CCVM previo al procedimiento quirúrgico. Posteriormente, los biomarcadores pueden utilizarse para guiar o sugerir intervenciones perioperatorias en los pacientes identificados como "de alto riesgo" que eviten o mejoren el control de las posibles CCVM. Finalmente, tal como recogen las guías y recomendaciones internacionales actuales (18), los biomarcadores cardíacos son la base del diagnóstico del daño miocárdico perioperatorio en cirugía no cardíaca (y, por extensión, también en la cirugía cardíaca), ya se trate de daño miocárdico poco extenso o de IM.

En la actualidad, los biomarcadores cardíacos más utilizados en cirugía no cardiaca son las troponinas cardiacas T y I (TncT y TncI), preferentemente medidas con métodos de alta sensibilidad, así como los péptidos natriuréticos de tipo B, que incluyen el BNP (*B-type natriuretic peptide*) y el NT-proBNP (*N-terminal prohormone of B-type natriuretic peptide*) que se han recomendado como predictores preoperatorios de complicaciones perioperatorias (19).

Un biomarcador cardíaco debe reunir algunas características para ser considerado como ideal. Debe de ser fácil de medir en cualquier tipo de laboratorio que atienda diagnósticos que involucren el uso del biomarcador. Su medida debe ser exacta, ya que se suelen referir a “valores de decisión clínica” específicos (p.ej. un límite superior de referencia) y una infra o supra valoración puede provocar diagnósticos falsamente negativos o positivos. La medida del biomarcador también ha de ser precisa, ya que se suelen utilizar en la clínica en determinaciones seriadas; una elevada imprecisión inducirá dudas diagnósticas. En un contexto de medicina socializada y universalizada, la medida del biomarcador ha de ser económicamente asequible para que no existan restricciones a su uso siempre que sea necesario. Finalmente, y muy importante, el biomarcador ha de ser, idealmente, totalmente o lo más específico posible del proceso fisiopatológico que se desee evaluar; un biomarcador específico permite reconocer un hecho fisiopatológico más precozmente que un biomarcador no completamente

específico. Como se ha comentado, a pesar de las diferencias en la terminología empleada para la definición de LMP y los diferentes enfoques sugeridos para su diagnóstico, existe un acuerdo general en la comunidad de la medicina perioperatoria de que el biomarcador ideal para la detección de LMP es la Tnc porque satisface las características comentadas prácticamente al 100%.

La troponina cardiaca desempeña un papel esencial en las células del músculo estriado al facilitar la interacción entre los filamentos de actina y miosina para la contracción muscular. La troponina consta de tres subunidades diferentes: la troponina C, que se une al calcio; la troponina T, que se une a la tropomiosina; y la troponina I, que regula la actividad de la ATPasa. Cada una de estas subunidades presenta variantes específicas en forma de isoformas, dependiendo del tipo de fibra muscular al que pertenecen. **(Figura 2).**

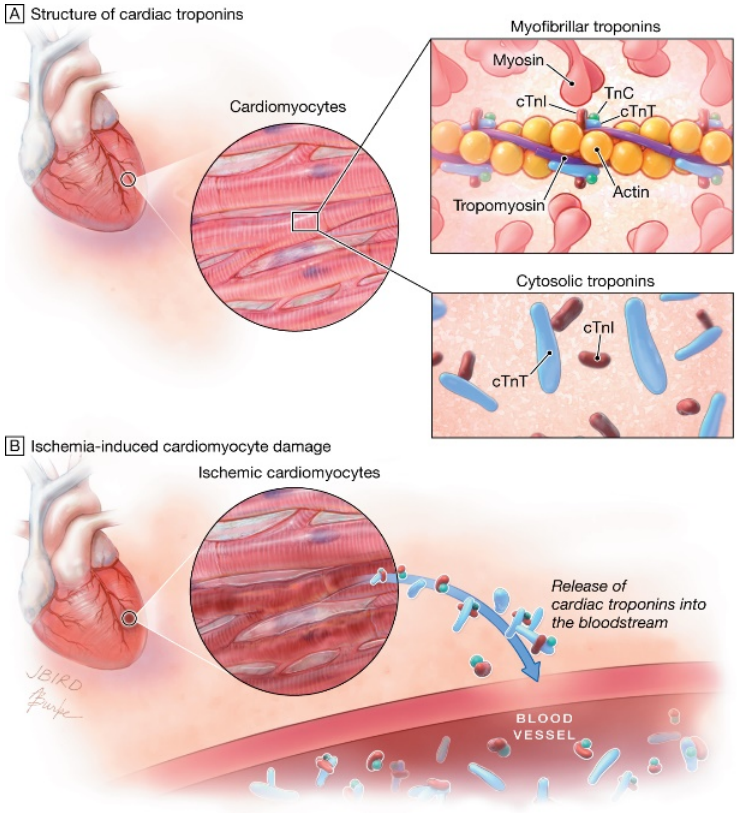

Figura 2. Isoformas de troponina y secreción tras isquemia.
Fuente: JAMA. 2013; 309(21):2262-2269. doi:10.1001/jama.2013.5809.

Es importante tener en cuenta que la troponina C es idéntica tanto en el músculo cardíaco como en el esquelético; esto limita su especificidad en la detección de las lesiones cardíacas. Por su parte, tanto la troponina T como la troponina I tienen isoformas altamente cardio-específicas, por lo que su detección en circulación proporciona una información inequívoca de las lesiones que afectan al tejido miocárdico (20).

Las Tnc se miden con inmunoensayos que utilizan anticuerpos que interactúan específicamente con cada subunidad T o I. Estos inmunoensayos han experimentado cambios significativos a lo largo de los últimos años, con el objetivo de lograr una mayor sensibilidad analítica para detectar concentraciones de TncT o TncI cada vez más bajas (21-22). En la actualidad, existen métodos denominados de alta sensibilidad (también denominados ultrasensibles) que detectan concentraciones de troponina decenas de veces inferiores a las detectadas por los primeros inmunoensayos desarrollados en el año 1989 para TncT (23) y en el año 1992 para TncI (24).

Las concentraciones medidas en circulación de TncT y TncI pueden variar según los diversos métodos comercialmente disponibles para su medida. En el caso de la TncT, los inmunoensayos disponibles utilizan mayoritariamente los mismos anticuerpos; por ello, la concentración con valor “diagnóstico” es la misma para los diferentes métodos. No ocurre lo mismo para la medida de TncI; los anticuerpos de los inmunoensayos varían entre los diferentes métodos; en consecuencia, la concentración “diagnóstica” es específica de cada inmunoensayo y diferente a la de otros métodos, aunque midan la misma molécula.

1.3.3. El cribado sistemático de la LMP. Métodos de utilización de TncT-as

Según la Organización Mundial de la Salud (OMS), el cribado de una condición de salud se define como "la identificación presuntiva de enfermedades o defectos no reconocidos, a través de la aplicación de pruebas, exámenes u otros procedimientos que pueden llevarse a cabo de manera rápida", con el propósito de "diferenciar entre las personas aparentemente sanas que probablemente padecen una enfermedad y aquellas que probablemente no la tienen"(25). Los programas de cribado se dividen en dos categorías según su objetivo: la detección de casos y el enfoque epidemiológico. La finalidad de la detección de casos es "identificar la enfermedad y guiar a los pacientes hacia el tratamiento", a diferencia del enfoque epidemiológico, que tiene la intención de "explorar la prevalencia, la incidencia y la historia natural de la variable o variables objeto de estudio”.

En 1968, la OMS propuso un conjunto de criterios para evaluar la idoneidad de un programa de cribado. Estos programas deben cumplir ciertos requisitos clave, como, por ejemplo: la condición estudiada debe ser un problema de salud importante, deben existir instalaciones disponibles para el diagnóstico y el tratamiento, se debe realizar una prueba o examen adecuado, la prueba debería ser aceptable para la población, ser eficiente y equilibrarse económicamente en relación con los posibles gastos en atención médica en su conjunto (25). Debido a que la LMP es mayoritariamente asintomática, el cribado sistemático con Tnc, especialmente si esta es medida con métodos de alta sensibilidad, resulta la estrategia más adecuada para su detección temprana. Debido al mal pronóstico asociado con la LMP, en los últimos años se ha observado un creciente interés por esta condición que se ha reflejado en guías de práctica clínica de cardiología y anestesia internacionales (18-19,26-33). Estas guías recomiendan de forma reiterada el cribado sistemático del daño miocárdico en cirugía no cardíaca mediante la medida de Tnc con métodos de alta sensibilidad desde que están disponibles, en lugar de basar la evaluación del daño miocárdico únicamente en los síntomas clínicos. Hay un creciente número de centros hospitalarios en Norteamérica y Europa que están empezando a integrar el cribado del LMP con Tnc en su rutina clínica habitual. Sin embargo, por el momento, disponemos de pocos ejemplos de la implementación del cribado sistemático en nuestro país.

Centrándonos a nivel nacional, en el año 2023, un equipo de investigadores de un hospital terciario español incluyó a 732 pacientes de ≥45 años sometidos a cirugía no cardíaca de diferentes especialidades y con riesgo intermedio-alto de CCVM (34). A estos pacientes se les realizaron mediciones de la troponina TncT-as y NT-proBNP antes de la cirugía, así como mediciones de la TncT-as en los tres primeros días postoperatorios. Las mediciones de biomarcadores cardíacos se llevaron a cabo en pacientes seleccionados en el marco del proyecto de investigación. Los autores concluyeron que un valor preoperatorio de TncT-as ≥14 ng/L, la concentración recomendada como límite superior de referencia en población sana, indicaba la necesidad de seguir midiendo TncT-as en el postoperatorio. En el caso de los pacientes con un valor basal de TncT-as <14 ng/L, un modelo de 6 variables (edad, género, FGe, capacidad funcional <4 METs o desconocida, NT-proBNP ≥300 ng/L y sangrado intraoperatorio) permitió identificar a pacientes adicionales con riesgo de LMP aguda, quienes también se podían beneficiar de las mediciones postoperatorias de TncT-as.

Otro estudio realizado en otro hospital terciario español incluyó a 177 pacientes sometidos a cirugía torácica electiva (35). Los pacientes incluidos presentaban factores de riesgo CV como edad ≥65 años, o, si eran más jóvenes, debían presentar alguno de los siguientes criterios: historia de enfermedad vascular periférica, EAC o AVC. En los dos días posteriores a la cirugía, a los pacientes se les realizaron mediciones de TncI con métodos contemporáneos, no de alta sensibilidad. Aquellos pacientes que presentaban valores elevados de TncI recibían un seguimiento por parte de anestesiólogos experimentados, quienes descartaban las causas no isquémicas de elevación de TncI (sepsis, EP, cardioversión), realizaban un ECG de control y solicitaban una consulta cardiológica. El estudio observó una incidencia elevada de LMP (27,3%) en este grupo específico de pacientes sometidos a cirugía torácica, una relación independiente entre la concentración de TncI con la extensión de la resección pulmonar y que la LMP no se asociaba con una mayor mortalidad. El estudio concluyó que, en este tipo de cirugía, las causas no isquémicas podrían contribuir a las elevaciones de TncI.

Ambos estudios son ejemplos de la diversidad de protocolos de evaluación, tipología de los pacientes y, no menos importante, de los métodos de Tnc utilizados para llevar a cabo el cribado de la LMP en cirugía no cardiaca. Por otra parte, los dos estudios confirman el interés y la sensibilidad del tema en nuestro entorno. Se necesitan más estudios que sirvan como ejemplos de experiencias locales, revelando todas las dificultades que puede conllevar la óptima y rigurosa implementación del cribado sistemático, teniendo en cuenta los recursos limitados de la sanidad pública nacional y la necesidad de su asignación más eficiente.

1.4. Uso de evaluaciones económicas en la salud

El objetivo de las evaluaciones económicas en salud es comparar los costes y las consecuencias de las tecnologías sanitarias existentes o novedosas frente a las de sus alternativas habituales para informar sobre el valor de la comparación (36).

Las evaluaciones económicas en salud se dividen en dos categorías: evaluación del coste-efectividad y evaluación del coste-beneficio. Aunque ambas evaluaciones utilizan métodos similares para definir y evaluar los costes económicos, se diferencian en cómo se evalúan las consecuencias de las tecnologías o tratamientos; por lo tanto, las conclusiones obtenidas pueden diferir entre ambos tipos de evaluación.

La herramienta ideal para llevar a cabo una evaluación económica debe ser integral. Esto significa que debe incorporar toda la evidencia científica disponible, considerar todas las alternativas de decisión pertinentes y tener en cuenta todas las consecuencias presentes y futuras de su implementación.

1.4.1. Eficiencia y evaluación económica de los procedimientos médicos

La evaluación económica en medicina es esencial para asegurar que los recursos, siempre limitados, de los sistemas de salud pública se utilicen de manera más eficiente. Esto conduce a una atención médica de mayor calidad, una asignación más justa de los recursos y un acceso mejorado a los servicios de salud. Según la OMS, la gestión correcta de recursos de un programa de cribado requiere un equilibrio entre los beneficios y los costes; esto significa que "el coste de la búsqueda de casos debe estar económicamente equilibrado en relación con los posibles gastos en atención médica en su conjunto" (25).

En la economía de la salud, para el análisis de coste-efectividad, que contribuye a la toma de decisiones terapéuticas, se emplea un concepto crucial como la relación (ratio) de coste-efectividad incremental (*Incremental Cost-Effectiveness Ratio - ICER*). ICER se utiliza para determinar la eficiencia de una nueva intervención o tratamiento médico en comparación con uno ya existente. Su fórmula es la siguiente: ICER (C1 - C2) / (E1 - E2), donde C1 y E1 son el coste y efecto del nuevo grupo de intervención o tratamiento y C2 y E2 el coste y efecto del comparador **(Figura 3.).**

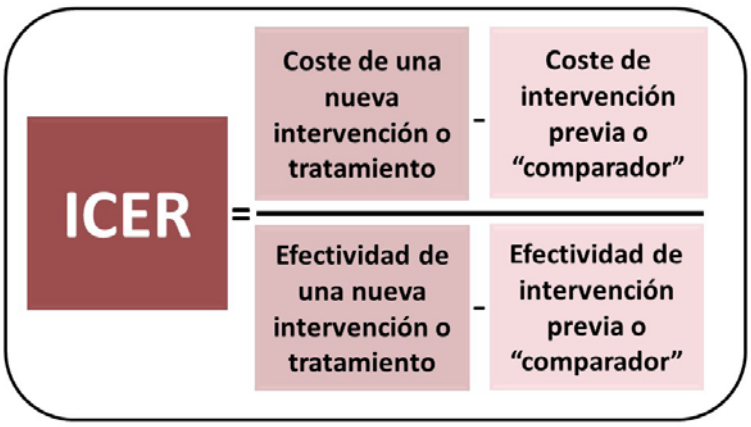

Figura 3. Formula de ICER.

Específicamente, el ICER proporciona una medida de cuánto cuesta económicamente lograr una mejora adicional en términos de salud al cambiar una intervención por otra y compararlas. Cuanto más bajo sea el valor del ICER, más eficiente será la nueva estrategia en términos de coste-efectividad, lo que significa que se requiere un menor coste adicional para lograr un beneficio añadido en salud respecto a la intervención previa. En el caso de elección de la intervención previa o "comparador", el más adecuado sería la "atención habitual"; es decir, la intervención más utilizada en la práctica clínica diaria en el contexto de la población estudiada. Los comparadores deben estar claramente identificados y justificados con suficiente detalle para que se pueda evaluar su relevancia. La elección del comparador determinará de manera crítica el coste-efectividad relativa de la nueva intervención (36-38). El horizonte temporal del período de realización del estudio de coste-efectividad también debe estar claramente definido y ser adecuado a la condición estudiada; debe ser suficientemente largo para poder identificar diferencias significativas en los costes y los resultados entre los comparadores (33).

1.4.2. Coste-efectividad del cribado sistemático de LMP con TncT-as

A pesar de la importancia de la detección de la LMP mediante el cribado sistemático con TncT-as y de las recomendaciones de las guías clínicas más actuales (18), el coste-efectividad de su utilización sistemática ha sido poco evaluado. Existen escasos estudios observacionales sobre este tema y no se dispone de resultados generados en ensayos clínicos aleatorizados o en metaanálisis.

Hasta la fecha, solo existen tres estudios que han evaluado el coste-efectividad del cribado con Tnc. Uno de ellos, fue realizado en el año 2007 (39), donde se utilizó un modelo de análisis de decisiones, basado en el modelo de Markov. El modelo fue diseñado para determinar el coste-efectividad del cribado sistemático con Tnc, medida con métodos contemporáneos, durante 4 días, incluyendo el mismo día de la cirugía (días 0, 1, 2 y 3) y evaluar los años de vida ajustados por calidad (*Quality-Adjusted Life Year - QALY*). El estudio incluyó a pacientes ≥65 años que fueron sometidos a la reparación abierta de aneurisma aortoabdominal, con el horizonte temporal de toda su vida restante. Los autores concluyeron que el cribado con TncI después de la reparación abierta de un aneurisma aortoabdominal era coste-efectivo en este grupo de pacientes, con el valor de Relación de Coste-Efectividad Incremental (ICER, por sus siglas en inglés) de $12,641/QALY.

Posteriormente, en el año 2014, Torborg (40) describió un análisis fármaco-económico para determinar el coste-efectividad del cribado postoperatorio con TncT, medida con métodos contemporáneos, en pacientes ≥45 años intervenidos de cirugía no cardíaca. La TncT se midió durante los 3 primeros días postoperatorios (días 1, 2 y 3). El coste incremental total de cribado y el tratamiento con aspirina y estatina fue 320,86 rand sudafricano/paciente. Los autores concluyeron que el cribado sistemático era

potencialmente coste-efectivo al iniciar el tratamiento con aspirina y estatinas en los pacientes con niveles elevados de TncT.

Finalmente, en 2018, Lurati Buse y colaboradores (41) desarrollaron un análisis de coste-consecuencia (una variación del análisis coste-efectividad que informa sobre varios criterios de valoración clínicos a la vez en lugar de uno único), en el que incluyeron a pacientes canadienses que participaron en el estudio VISION (≥45 años sometidos a cirugía no cardíaca con, al menos, una noche de hospitalización). Este estudio, a diferencia de los dos anteriormente mencionados, incluyó una gran cohorte de pacientes (6021 casos) sometidos a un amplio espectro de procedimientos de cirugía no cardíaca. Se midió TncT con métodos contemporáneos en cuatro ocasiones, incluyendo el mismo día de la cirugía (entre 6 y 12 horas después de la cirugía) y en los días 1, 2 y 3 del postoperatorio. El coste incremental estimado para detectar un caso adicional de MINS fue inferior a $1,350 (dólares canadienses). Los autores concluyeron que los costes asociados con el cribado sistemático de TncT eran moderados y que su implementación era potencialmente coste-efectiva, especialmente en pacientes con alto riesgo CV.

Los tres estudios descritos han mostrado resultados comparables, independientemente de que se hayan realizado en diferentes poblaciones y sistemas sanitarios, se hayan empleado métodos de detección de Tnc con diferente sensibilidad analítica, se hayan medido TncI o TncT y, finalmente, se hayan utilizado diferentes enfoques y análisis económicos. Las conclusiones coinciden en que el cribado sistemático con Tnc en pacientes sometidos a cirugía no cardiaca es coste-efectivo, especialmente en los de alto riesgo.

1.5. Etiología de LMP

Las lesiones miocárdicas ocurren mayoritariamente por fenómenos isquémicos. La isquemia miocárdica se produce cuando existe un desequilibrio entre la demanda y el aporte de oxígeno (O_2) al miocardio; el desequilibrio puede ser causado por aterotrombosis coronaria, que por analogía con la definición de IM se clasifica como “isquemia tipo 1” o cuando las arterias coronarias son permeables y la isquemia no puede atribuirse a la aterotrombosis se denomina como “isquemia tipo 2” (42). La LMP puede ser causada por aterotrombosis, pero también pueden estar involucradas numerosas condiciones peri- o postoperatorias (43). Entre estas últimas se pueden citar el estrés quirúrgico, la manipulación de vasos sanguíneos, la hipotensión, la anemia y la inflamación/infecciones sistémicas asociadas a los procedimientos quirúrgicos, los trastornos de ritmo cardíaco como la FA (44) o causas no cardíacas como la embolia pulmonar (EP) (45). Todos estos datos sugieren que la LMP es de naturaleza multifactorial y puede ser desencadenada tanto por un único factor de los mencionados como por la combinación de varios de ellos. Por lo tanto, la identificación de las causas de la LMP no es una tarea sencilla.

Un estudio reciente que incluyó un total de 10 772 pacientes consecutivos sometidos a cirugía mayor no cardíaca en dos hospitales en Suiza y uno en Brasil, que tuvieron una estancia postoperatoria ≥2 días, se propuso clasificar las etiologías de las LMP detectadas en el curso de un cribado sistemático, utilizando TncT-as en Suiza y TncI-as en Brasil (43). Las etiologías fueron adjudicadas por dos investigadores médicos independientes, con el apoyo de segundas y terceras opiniones en los casos de discrepancias, utilizando

toda la información obtenida durante la evaluación clínica, incluyendo imágenes cardíacas. La LMP se detectó en 13,1% de casos y los investigadores las clasificaron etiológicamente en "extracardíacas" (sepsis, EP, otras causas) o "cardíacas"; estas últimas, a su vez, fueron subdivididas en IM tipo 1 o isquemia de tipo2, taquiarritmias e insuficiencia cardíaca aguda. La isquemia tipo 2 se observó en tres de cada cuatro LMP y fue 10 veces más frecuente que la isquemia tipo 1 de origen aterotrombótico **(Figura 4)**.

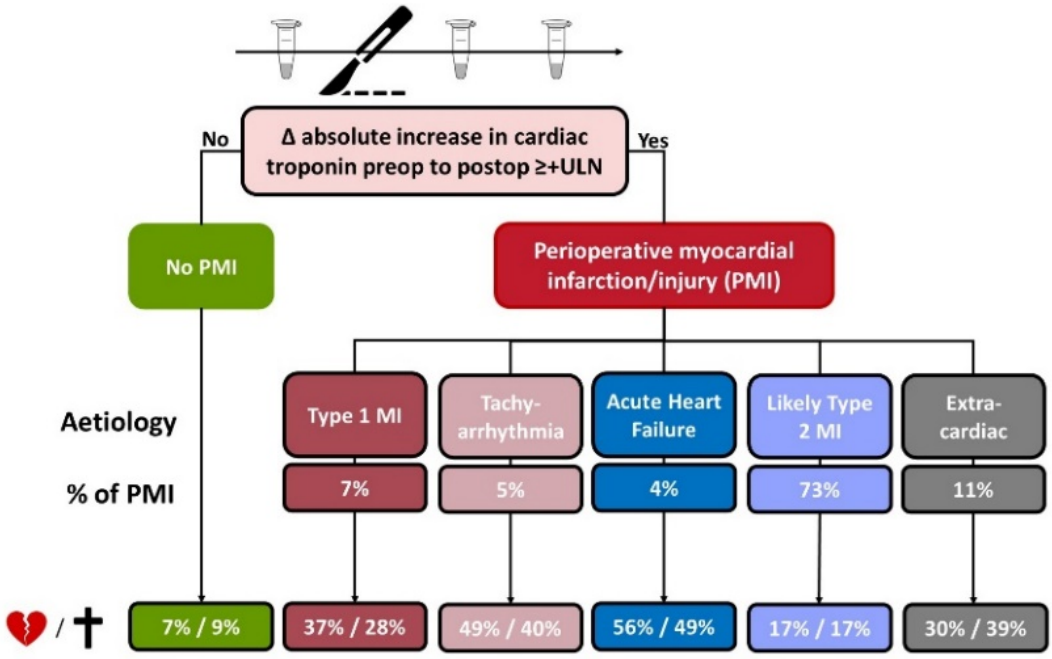

Figura 4. Etiologías de LMP (referida como PMI).
Fuente (figura adaptada): Eur. Heart J. 2023 May 14;44(19):1690-1701. doi: 10.1093/eurheartj/ehac798.

Notablemente, las LMP de origen isquémico tipo 2 presentaron menos morbilidad CV y mortalidad total en el seguimiento que el resto de las etiologías. Dada esta diferencia en la proporción de complicaciones, resulta muy importante identificar la etiología que provoca la LMP para la mejor gestión clínica y personalización del tratamiento de cada subgrupo de estos pacientes

1.5.1. Pruebas avanzadas de imagen cardiaca

Actualmente, las pruebas avanzadas de imagen cardíaca constituyen herramientas imprescindibles para comprender las causas de las alteraciones miocárdicas. Estas pruebas de imagen son ideales para descartar enfermedades coronarias en pacientes con bajo o moderado riesgo CV, para el estudio pre y postquirúrgico de pacientes adultos que se someten a cirugías y para evaluar la permeabilidad de los injertos aorto-coronarios (*by-pass*). Actualmente, el portafolio de pruebas de imagen cardíaca en los centros sanitarios terciarios incluye la tomografía computarizada cardíaca (TCC) y la resonancia magnética cardíaca (RMC).

Dado el creciente interés en la etiología de la LMP, las pruebas diagnósticas avanzadas y mínimamente invasivas, como la TCC y la RMC, pueden ofrecer información sumamente relevante para identificar la etiología, evaluar cambios estructurales en el tejido cardíaco, así como para evaluar la perfusión y función contráctil miocárdicas. Se ha demostrado que la TCC mejora la eficacia diagnóstica y pronóstica del “Índice de Riesgo Cardíaco Revisado” (IRCR) (46), un indicador recomendado para detectar eventos cardíacos graves tras la cirugía no cardiaca y pronosticar la futura evolución de los pacientes con estos eventos; mientras que la RMC se considera el "estándar de oro" para la evaluación no invasiva de la funcionalidad del miocardio.

1.5.2. TCC y RMC en la fisiopatología de la LMP

A pesar de que la TCC y la RMC pueden proporcionar información muy relevante para comprender la fisiopatología de LMP, su realización en la práctica clínica en pacientes sometidos a cirugía no cardíaca con LMP confirmada o sospechada puede no solo ser compleja, sino sobre todo costosa (44). Actualmente, existen pocos estudios que hayan aplicado estas pruebas de imagen cardiaca en el contexto perioperatorio (47). Uno de los primeros fue el estudio OPTIMUS (48), que incluyó a 30 pacientes con IM perioperatorio tras cirugía no cardíaca y a 30 pacientes con IM no quirúrgico. A los pacientes se les practicó una tomografía de coherencia óptica (TCO) intracoronaria. A pesar de que la morfología de las placas arterioscleróticas detectadas en la TCO era similar en ambos grupos, la trombosis se detectó en un 12% de los casos que sufrieron el IM perioperatorio, mientras que esta etiología se detectó en dos de cada tres (66%) pacientes que sufrieron el IM no quirúrgico. Grobben (42) realizó un estudio prospectivo de cohortes que incluyó pacientes de edad ≥60 años de riesgo intermedio-alto, pero sin antecedentes de enfermedad cardiaca que fueron sometidos a cirugía no cardiaca. La LMP se definió como cualquier nivel de TncI ≥60 ng/L (método contemporáneo) en los tres primeros días postoperatorios. Los autores observaron la existencia de una asociación de LMP con EAC, así como la existencia de EP clínicamente silente en un tercio de los pacientes con LMP. Posteriormente, el estudio VISION-CTA (49) (subestudio de la cohorte VISION) incluyó a 55 pacientes (con los mismos

criterios del cribado de TncT y definición de LMP que el protocolo del estudio), a quienes se les realizó la TCC y un estudio de perfusión miocárdica con radionúclidos, como parte de su evaluación preoperatoria. Los resultados del estudio generaron la hipótesis de que el riesgo perioperatorio puede refinarse empleando la perfusión miocárdica con radionúclidos en los pacientes con enfermedad obstructiva coronaria detectada por TCC.

Los resultados de todos estos estudios coinciden en la necesidad de conocer mejor las causas etiopatogénicas que provocan la LMP; el conocimiento de estas causas podría ayudar a desarrollar intervenciones preventivas y/o terapéuticas que mejoren la evolución clínica inmediata y a largo plazo en estos pacientes.

1.6. Justificación del tema de investigación de la tesis

Como se mencionó anteriormente, las guías internacionales más recientes (18) indican que el cribado sistemático con Tnc es el primer paso en el proceso integral para la detección, diagnóstico y atención clínica adecuados de los pacientes que presentan LMP. No obstante, la publicación y difusión de guías o recomendaciones no siempre garantizan su inmediata adopción en la práctica clínica habitual debido a los numerosos retos y dificultades que puede suponer su implementación.

A pesar de la importancia de la detección de la LMP mediante el cribado sistemático con Tnc (sobre todo si está medida con métodos de alta sensibilidad), hay escasa información sobre su coste-efectividad, que podría facilitar la priorización y asignación de recursos asistenciales de manera más eficiente.

Por último, un mejor conocimiento de las causas fisiopatológicas de la LMP podría representar el siguiente paso para personalizar el manejo clínico y el tratamiento más apropiado de los pacientes con LMP, donde las pruebas de imagen cardíaca avanzada, como la TCC y la RMC, pueden ser las mejores aliadas.

En consecuencia, la presente tesis se ha desarrollado en torno a tres acciones principales con sus correspondientes estudios, con el objetivo de adquirir un mayor conocimiento y dar continuidad a estas tres líneas de investigación en nuestro medio. Los estudios se representan en la **Figura 5.**

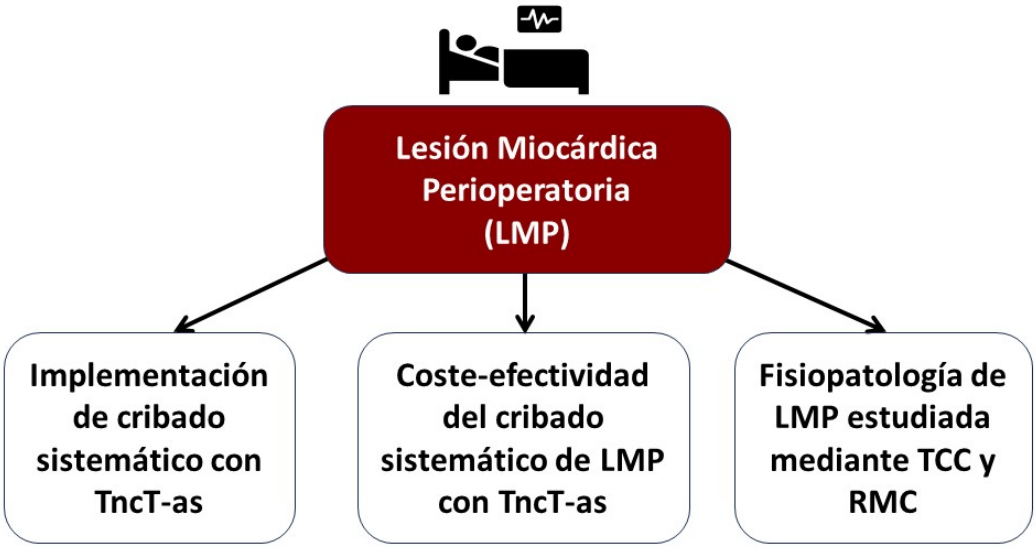

Figura 5. Estructura de la tesis.

2. OBJETIVOS

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2.1. Objetivo general

El objetivo general de la presente tesis doctoral ha sido investigar la LMP en pacientes con riesgo CV elevado, sometidos a cirugía mayor no cardíaca en hospitales terciarios españoles y evaluar:

- Los resultados obtenidos durante la implementación de su cribado sistemático mediante la medición de TncT-as.
- El coste-efectividad del citado cribado sistemático de la LMP con de TncT-as, comparado con la práctica clínica habitual.
- La utilidad de las pruebas avanzadas de imagen cardiaca, como TCC y la RMC, para la identificación de las causas fisiopatológicas de la LMP y su influencia en las CCVM durante el seguimiento postoperatorio.

2.2. Objetivos específicos

Del estudio I:

- Determinar las barreras y facilidades del proceso de la implementación del cribado sistemático.
- Determinar la prevalencia de LMP en un hospital español, universitario, de tercer nivel.
- Determinar la relación entre las concentraciones de TncT-as, las CCVM y la mortalidad a los 30 días y al año después de la cirugía.
- Determinar la incidencia de los componentes individuales de las CCVM y la mortalidad a los 30 días y al año después de la cirugía.

Del estudio II:

- Determinar si la ratio coste-efectividad incremental (ICER) del cribado de la LMP, incluyendo TncT-as, justifica su implementación sistemática en la práctica clínica habitual.

Del estudio III:

- Determinar la prevalencia de EAC entre pacientes con LMP y pacientes control.
- Determinar la incidencia de las CCVM al año después de la cirugía y su relación con EAC.
- Determinar la incidencia de los componentes individuales de las CCVM y su relación con la mortalidad en el seguimiento al año después de la cirugía.

3. MÉTODOS

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El trabajo de tesis, que se presenta como un compendio de publicaciones, se basa en tres estudios desarrollados, y la metodología empleada se describe para cada uno de ellos a continuación.

3.1. ESTUDIO I: Importancia de la implementación del cribado sistemático del daño miocárdico perioperatorio en pacientes intervenidos de cirugía mayor no cardiaca

3.1.1. Diseño del estudio

El estudio I, consistió en un estudio de cohorte prospectivo y observacional, realizado en un centro universitario español de tercer nivel (Hospital de la Santa Creu i Sant Pau, Barcelona). El protocolo del estudio se publicó en la plataforma de acceso abierto de publicación de trabajos de investigación - *F1000Research* (50).

3.1.2. Población del estudio y criterios de elegibilidad

El estudio se realizó desde julio del año 2016 a marzo del 2019 e incluyó pacientes quirúrgicos con alto riesgo CV preoperatorio que se sometieron a cirugía mayor no cardiaca programada o urgente y requirieron al menos una noche de ingreso en el hospital.

Los criterios de inclusión fueron: edad ≥65 años o, si esta era <65 años, presentar al menos alguno de los siguientes antecedentes cardiovasculares: EAC, ICC, AVC, accidente isquémico transitorio (AIT), o enfermedad vascular periférica. También se incluyeron aquellos pacientes con deterioro de la función renal (tasa de FGe <60 mL/min/1,73 m^2). Las intervenciones quirúrgicas mayores no cardíacas incluidas fueron las ortopédicas, traumatológicas, neuroquirúrgicas de columna, viscerales, digestivas, vasculares periféricas, torácicas, ginecológicas, plásticas u otorrinolaringológicas. Se excluyeron los pacientes <65 años sin antecedentes de enfermedades CV; así como aquellos sometidos a cirugías menores y los operados durante fines de semana o días festivos, independientemente de su edad. También se excluyeron los pacientes incapaces de comprender el protocolo y/o firmar el consentimiento informado.

3.1.3. Metodología del estudio

En todos los pacientes incluidos se realizaron tres mediciones de TncT-as: antes de la cirugía (en la visita preoperatoria o inmediatamente antes de la intervención quirúrgica) y a las 48 y 72 horas de esta. En el caso de las cirugías electivas, las mediciones preoperatorias de TncT-as fueron solicitadas por los

cirujanos y/o anestesiólogos que realizaban las visitas preoperatorias. En el caso de cirugías urgentes, las peticiones fueron solicitadas por los cirujanos y/o anestesiólogos a cargo o, si no se habían cursado, se determinaron a partir de alícuotas de plasma almacenadas a 4 °C en el laboratorio clínico durante no más de 24 horas. Las mediciones postoperatorias de TncT-as fueron solicitadas por los médicos responsables de los pacientes con el apoyo del servicio de epidemiología clínica.

La TncT-as se midió mediante un inmunoensayo electroquimioluminiscente (*Roche Diagnostics, Basel, Switzerland*) que ofrece un intervalo de medición de 5-10 000 ng/L y un límite de detección de 5 ng/L. El percentil 99 de referencia consensuado y recomendado es de 14 ng/L y una concentración de 13 ng/L se mide con un 10% de variación analítica. Se ha demostrado que el método mide TncT-as por encima del límite de detección en más del 50% de sujetos sanos. Por lo tanto, el método cumple los requisitos analíticos para ser considerado como de alta sensibilidad (51). En el laboratorio de Bioquímica del Hospital de la Santa Creu i Sant Pau se mide la TncT-as 24 horas al día, 7 días por semana y la calidad analítica de las determinaciones se controla en programas internos y externos nacionales e internacionales.

El criterio para definir la LMP se estableció basándose en la bibliografía disponible en el momento del desarrollo del protocolo del estudio (52) y teniendo en cuenta la experiencia previa del equipo investigador (9,16). La LMP se definió como un valor postoperatorio de TncT-as ≥14 ng/L, con un aumento del ≥50% sobre el valor preoperatorio. El IM se definió con los criterios de la tercera definición universal del mismo (53), ya que el protocolo se diseñó a finales del año 2015 y el estudio se inició el mes de Julio del año 2016; la Cuarta Definición Universal de IM no se publicó hasta finales del año 2018 (54).

Cuando se observaba la existencia de LMP, de acuerdo con las concentraciones elevadas de TncT-as en el postoperatorio, se procedía a una evaluación cardiológica formal del paciente por un cardiólogo consultor. Este proceso incluía la revisión de datos clínicos, tales como signos y síntomas específicos existentes, así como la realización de un ECG de control postoperatorio para compararlo con el preoperatorio. Además, se realizaba un ecocardiograma con el objetivo de detectar posibles alteraciones de la contractilidad miocárdica. La exclusión de la LMP o su atribución a factores no isquémicos o no cardíacos, como antecedentes de cardioversión o la presencia de EP o sepsis, se determinaba por los cardiólogos consultores. También se llevaba a cabo una revisión o ajuste del uso de medicamentos con acción CV, como aspirina, otros antiagregantes plaquetarios, inhibidores de la enzima convertidora de angiotensina (IECAs), estatinas, betabloqueantes y anticoagulantes orales.

Finalmente, se evaluaba la necesidad de realizar otros procedimientos diagnósticos o terapéuticos, como la angiografía coronaria y/o la revascularización cardíaca. En caso de ser necesarios, estos procedimientos eran prescritos por el cardiólogo consultor.

3.1.4. Seguimiento de los pacientes

Todos los pacientes incluidos en el estudio recibieron un seguimiento presencial durante los tres primeros días de hospitalización posteriores a la cirugía, así como un seguimiento telefónico al mes y al año tras la intervención.

Con el fin de homogeneizar las definiciones de las complicaciones más relevantes relacionadas con el procedimiento quirúrgico o durante el postoperatorio inmediato (primeras 72 horas post cirugía), el equipo investigador acordó las siguientes definiciones:

- Hipotensión arterial significativa: un descenso del 30% de la presión arterial sistólica (PAS) con respecto al valor basal (antes de la inducción anestésica);
- Hipertensión arterial significativa: una presión arterial sistólica (PAS) >140 mmHg y/o presión arterial diastólica (PAD) >90 mm Hg;
- Taquicardia significativa: si la frecuencia cardiaca (FC) era >100 latidos por minuto (lpm);
- Bradicardia significativa: si la frecuencia cardiaca (FC) era <60 lpm;
- Sangrado significativo: medida postoperatoria de concentración de hemoglobina (Hb) <70 g/L + necesidad de transfusión de 2 concentrados de hematíes (CH) en 24 horas o un descenso de Hb de >50 g/L respecto al valor preoperatorio o necesidad transfusión de 3 o más (CH) en 24 horas
- Hipoxemia significativa: saturación de oxígeno (SaO_2) <90%.

En el informe de alta de los pacientes que habían presentado LMP se informaba de la existencia y características de esta o de un IM si este fuera el caso, se recomendaba un plan de seguimiento personalizado por su equipo asistencial habitual que, en función de las características del paciente incluía información sobre la existencia y diagnóstico de LMP o de IM, recomendaciones específicas para su atención clínica y revisión/actualización de su tratamiento farmacológico.

Las evaluaciones de seguimiento al mes y al año después de la cirugía fueron realizadas por el personal de investigación, desde el servicio de epidemiología clínica, mediante las llamadas telefónicas a los pacientes o a sus familiares cuando los pacientes no podían comunicarse. Durante las llamadas se consultaban los registros clínicos electrónicos para recopilar cualquier información relevante sobre las complicaciones CV no proporcionada por el paciente o familiar.

3.1.5. Obtención y gestión de los datos del estudio

Los datos registrados durante la hospitalización, así como obtenidos en los seguimientos telefónicos al mes y al año de la cirugía, se recogieron en cuadernos de recogida de datos (CRD) diseñados por el equipo investigador. Desde el formato de CRD en papel (que al finalizar el estudio se conserva y custodia en el Área de Gestión de Documentación de Ensayos Clínicos (AGDAC) del Hospital Sant Pau), los datos clínicos recogidos se transcribieron a una base de datos electrónica segura (www.clinapsis.com), preservando el anonimato de los pacientes y controlando la calidad e integridad de los datos. El acceso a la información de salud protegida como registros clínicos, documentos fuente, registros de visitas de seguimiento y datos de los CRDs se limitó exclusivamente a los miembros del equipo investigador mediante contraseña. Todos los procedimientos se ajustaron a lo contenido en la Ley Orgánica 1/1999, de 3 de diciembre, sobre la protección de datos de carácter personal.

3.1.6. Variables del estudio

Variables principales. Las variables principales evaluadas fueron la incidencia de mortalidad por cualquier causa y de CCVM en el plazo de un mes y de un año después de la cirugía.

Se definió como muerte por cualquier causa aquel fallecimiento claramente documentado como atribuible a una causa no CV, mientras que la muerte por causa CV se definió como el fallecimiento atribuible a causas CV o súbitas/desconocidas.

Se definió como CCVM al conjunto de diagnósticos de IM, ICC, nueva FA clínicamente relevante, AVC/AIT, EP o necesidad de revascularización cardiaca. Las definiciones de estos componentes individuales se basaron en las guías vigentes durante el periodo del estudio.

Variables secundarias. Las variables secundarias fueron los componentes individuales de la variable CCVM, con el objetivo de analizar su impacto individual en el evento compuesto CCVM. Además, se añadió como variable secundaria la infección postoperatoria, debido a su frecuencia y relevancia en la variable principal de mortalidad por cualquier causa.

La calidad global del proceso de implementación de cribado sistemático se evaluó mediante el porcentaje de casos en los que se completaron adecuadamente todas las fases del proceso.

3.1.7. Estadísticos descriptivos y análisis inferenciales

Las variables categóricas se presentaron como porcentajes y número de casos; las variables cuantitativas como media y desviación estándar, o mediana y rango intercuartílico de acuerdo con la distribución de los datos. La prevalencia y/o incidencia se describieron con sus respectivos intervalos de confianza del 95%. Las diferencias univariantes entre las variables independientes y las variables

principales (mortalidad por cualquier causa y CCVM) se evaluaron con análisis estadísticos como las pruebas chi-cuadrado, prueba exacta de Fisher, prueba "t" de Student o pruebas no paramétricas, según la naturaleza y/o distribución de la variable. Para evaluar la significación de las pruebas estadísticas, se aceptó una significación de $p<0,05$ (para prueba bilateral). El procesamiento de los datos y los análisis estadísticos se llevaron a cabo utilizando IBM-SPSS statistics, versión 29.0 (IBM Corp. Released 2023. IBM SPSS Statistics for Windows, Version 29.0. Armonk, NY: IBM Corp).

3.1.8. Consideraciones éticas

El protocolo de estudio fue aprobado por el Comité Ético de Investigación Clínica del Hospital de la Santa Creu i Sant Pau, Barcelona. El dictamen favorable se emitió el 11 de mayo de 2016 y el estudio fue identificado por un número único: IIBSP-IMP-2015-95. El estudio se desarrolló de acuerdo con los principios establecidos en la Declaración de Helsinki. Todos los participantes firmaron voluntariamente un consentimiento informado, manifestando su aceptación a participar en el estudio tras haber recibido la información del equipo investigador y haber formulado todas las preguntas o dudas sobre el estudio. El consentimiento se firmó anterior o lo más inmediatamente posible después de la intervención quirúrgica. Todos los pacientes fueron informados de su potestad para retirar su consentimiento en cualquier fase del estudio.

3.1.9. Financiación del estudio

El estudio fue financiado con una beca competitiva de investigación de la *Fundació La Marató de TV3* en el año 2015 *(La isquèmia miocàrdica perioperatòria: aplicació de monitorització de troponina, anàlisi econòmica i més coneixements en fisiopatología; expediente: 20150110*); otorgada a P. Alonso Coello como Investigador Principal, siendo E. Popova investigadora asociada del estudio.

3.2. ESTUDIO II: Coste-efectividad de la estrategia de cribado sistemático de troponina cardiaca T medida con alta sensibilidad comparada con la atención habitual para identificar pacientes con lesión miocárdica perioperatoria tras cirugía mayor no cardiaca

3.2.1. Diseño del estudio

El estudio II evaluó la relación coste-efectividad de una estrategia de cribado sistemático de la LMP con TncT-as, en pacientes con riesgo CV elevado, comparándolo con el de la atención habitual (sin incluir el cribado). El estudio se basó en la misma cohorte de los 1477 pacientes que participaron en el estudio I.

3.2.2. Población del estudio y criterios de elegibilidad

Los criterios de inclusión o exclusión y las características de los pacientes integrados en las estrategias de cribado sistemático con TncT-as o de atención habitual son los descritos en el apartado **3.1.2.**

En la rama de atención habitual, se consideró que los mismos 1477 pacientes incluidos en la estrategia de cribado sistemático constituían una cohorte hipotética de comparación, asumiendo que la identificación de la LMP se habría basado en la existencia de signos o síntomas isquémicos cardíacos y que las mediciones de TncT-as se habrían realizado solo cuando se hubieran detectado estos signos o síntomas.

3.2.3. Modelo del estudio

Se diseñó un árbol de decisión comparando la efectividad y los costes del cribado sistemático (con TncT-as) con la atención habitual. El estudio se realizó con un horizonte temporal corto, de 30 días postcirugía y desde la perspectiva del "pagador" (Sistema Nacional de Salud). Es decir, solo se consideraron los costes directos de la atención sanitaria y no se incluyeron ni costes indirectos (pérdidas de productividad a consecuencia de la enfermedad) ni otros costes de los pacientes y de sus acompañantes (básicamente los costes de desplazamiento y los costes del tiempo invertido) que hubiesen sido considerados de elaborarse el estudio desde una perspectiva social.

Los datos de efectividad en el grupo de intervención se estimaron utilizando como criterio de valoración los casos de LMP detectados en la cohorte del estudio. La efectividad de la estrategia de atención habitual se evaluó, como se ha comentado, en una cohorte hipotética que incluyó a los mismos pacientes incluidos en el cribado sistemático con TncT-as, pero en los que solo se hubiera procedido al protocolo de cribado si se hubieran presentado signos y síntomas. La incidencia de LPM y el número de procedimientos realizados se obtuvieron de la cohorte del estudio. La información sobre los costes se obtuvo del departamento de contabilidad del Hospital de la Santa Creu i Sant Pau, Barcelona y de la

información públicamente disponible del Departament de Salut, Generalitat de Catalunya. Todos los costes se calcularon con su valor en el año 2021 y se expresaron en euros (€).

Se calculó la Relación de Coste-Efectividad Incremental (ICER, por sus siglas en inglés) como el coste económico incremental de cada LMP detectada adicionalmente mediante la estrategia de cribado sistemático. La robustez del modelo de coste-efectividad se analizó mediante análisis de sensibilidad determinístico y probabilístico. El modelo económico fue ejecutado con el software TreeAge Pro, versión 2021 1.1.17 (TreeAge Software, LLC. PO Box 9946, Longboat Key; FL 34228, EE. UU) con el soporte de los expertos del Centro de Investigación en Economía y Sostenibilidad (ECO-SOS) de la Facultad de Economía de la Universitat Rovira I Virgili.

3.2.4. Características de las estrategias. Comparación

Estrategia de cribado sistemático con TncT-as

La estrategia de cribado sistemático definió cuatro posibles estados de salud:

1) verdaderos positivos (VP): LMP confirmada por elevación de TncT-as,

2) verdaderos negativos (VN): LMP excluida por ausencia de elevación de TncT-as,

3) falsos positivos (FP): Incremento de TncT-as por causas no isquémicas o no cardíacas, y

4) falsos negativos (FN): LMP confirmada en ausencia de elevación de TncT-as en el postoperatorio.

Los datos del estado de salud para la clasificación de los pacientes se obtuvieron durante el ingreso y en el seguimiento a los 30 días tras la cirugía.

Estrategia de Atención Habitual

En base a datos de un estudio similar llevado a cabo en Canadá (41), así como a la opinión de expertos locales, la estrategia de atención habitual también contempló cuatro posibles estados de salud:

1) verdaderos positivos (VP), pacientes en los que por presentar signos o síntomas de isquemia cardiaca la LMP se confirmó con pruebas diagnósticas,
2) verdaderos negativos (VN), pacientes que no presentaron signos o síntomas de LMP,
3) falsos positivos (FP), pacientes en los que se sospechó la LMP, pero no se confirmó con las pruebas diagnósticas,
4) falsos negativos (FN), pacientes que presentaron LMP durante periodo de observación (30 primeros días), sin sospecha inicial.

En esta estrategia, la evaluación de los pacientes ya sea con o sin sospecha clínica de LMP, se realizó con las pruebas diagnósticas siguiendo la práctica clínica habitual, en la que la medición de TncT-as solo se

llevaba a cabo para confirmar o descartar la isquemia miocárdica cuando se observaban signos o síntomas sospechosos de la misma. Se asumió que la incidencia de LMP sospechada por síntomas como dolor torácico o similares, pero sin afectación miocárdica, sería aproximadamente del 1% (41).

3.2.5. Utilización de recursos y estimación de costes

Los costes sanitarios directos incluyeron los costes de los procedimientos y tratamientos aplicados en ambas estrategias, así como el coste del tiempo empleado por los profesionales.

En la estrategia de cribado sistemático, se consideraron los costes de las pruebas de cribado (determinaciones de TncT-as), de confirmación diagnóstica (evaluación cardiológica formal, ECG y ecocardiografía), de las intervenciones adicionales requeridas, fundamentalmente coronarias, ya fueran únicamente angiografías diagnósticas o con intervención coronaria percutánea, y/o del tratamiento farmacológico previamente prescrito (aspirina y/o estatinas) o adicional y, finalmente de los costes del seguimiento a los 30 días de la intervención.

El uso de recursos para los cuatro estados de salud incluyó el coste de las determinaciones de TncT-as y del seguimiento a 30 días. Sin embargo, excepto en los verdaderos negativos (VN), los tres restantes estados de salud incorporaron otros costes adicionales. En el caso de los verdaderos positivos (VP), se sumaron los costes de la confirmación diagnóstica (evaluación cardiológica formal más ECG y ecocardiografía) y de las pruebas adicionales necesarias, con o sin tratamiento farmacológico, como de la angiografía diagnóstica o la intervención coronaria percutánea. En el caso de los falsos positivos (FP), se añadió el coste de la evaluación cardiológica formal, y en los falsos negativos (FN), se sumaron los costes de la confirmación diagnóstica y de las pruebas adicionales.

En la estrategia de atención habitual, como se mencionó anteriormente, no se midió sistemáticamente la TncT-as. Consecuentemente, en la evaluación económica no se incluyeron los costes de laboratorio ni los del seguimiento a los 30 días. En los casos de sospecha de LMP, confirmados como verdaderos positivos (VP) en la estrategia de cribado sistemático, se tuvieron en cuenta los costes de los siguientes recursos: confirmación diagnóstica (evaluación cardiológica formal más ECG y ecocardiografía), pruebas invasivas adicionales con o sin tratamiento (angiografía o intervención coronaria percutánea), y/o tratamiento farmacológico (aspirina y/o estatinas). Cuando se descartaba LMP por la ausencia de signos o síntomas isquémicos, en caso de falsos positivos (FP) en la estrategia de cribado, sólo se consideraba el coste de la confirmación diagnóstica. No se tuvieron en cuenta los costes para los verdaderos negativos (VN) ni para los falsos negativos (FN), ya que estos pacientes generalmente no recibían seguimiento en la estrategia de atención habitual.

En lo que respecta a los costes asociados al tratamiento farmacológico (aspirina y/o estatinas), se consideraron los costes de estos fármacos recetados durante el período de los primeros 30 días del postoperatorio, independientemente de si los pacientes ya estaban recibiendo este tratamiento previamente. En el momento del diseño del estudio, no existía una recomendación específica acerca del manejo farmacológico de los pacientes con LMP. Por lo tanto, la prescripción de estatinas y aspirina se basó en los factores de riesgo CV de los pacientes, según las guías disponibles en la fecha del estudio (27).

3.2.6. Análisis del estudio

Una vez calculados los costes y la efectividad de ambas estrategias, se obtuvo el resultado principal del estudio: la relación entre la diferencia de costes y la diferencia de efectividad (ICER). Dado que todos los parámetros incluidos en el análisis estaban sujetos a incertidumbre, posteriormente se procedió al análisis de sensibilidad determinista y probabilístico para evaluar la importancia de dicha incertidumbre sobre el resultado del ICER.

El análisis determinista (Tornado) asume un rango plausible de los valores de los parámetros incluidos en el análisis y presenta el impacto, de mayor a menor, sobre el valor del ICER.

El análisis probabilístico estima de forma conjunta la incertidumbre, aplicando distribuciones estadísticas a los parámetros incluidos en el análisis.

Análisis de sensibilidad determinista

Se realizaron dos análisis independientes de sensibilidad determinista mediante el diagrama Tornado. En el primer análisis, se incorporaron los valores predictivos positivos y negativos de ambas estrategias, considerando un rango plausible de variación (±1%) con respecto al valor introducido en el estudio. En el segundo análisis de Tornado, se incluyeron todos los parámetros de costes asociados a ambas estrategias. En este segundo análisis, se asignó una variación del ±15% a cada parámetro incluido.

Análisis de sensibilidad probabilístico

Se desarrolló un análisis de sensibilidad probabilístico mediante simulaciones de Monte Carlo de segundo orden. En este enfoque, todos los parámetros fueron variados simultáneamente de forma aleatoria en 10 000 iteraciones, generando distribuciones conjuntas de costes y efectos que reflejarían la incertidumbre del modelo analizado.

Los resultados de este análisis se resumieron utilizando la curva de aceptabilidad coste-eficacia recomendada (*CEAC - Cost-Effectiveness Acceptability Curve*) (55). CEAC representa el porcentaje de

iteraciones coste-efectivas en función de la disposición a pagar (*WTP - Willingness to pay*) para el coste del nuevo proceso que se evalúa.

Disposición a Pagar

La disposición a pagar (WTP) representa el coste máximo que la sociedad estaría dispuesta a asumir por cada caso adicional detectado. Hasta donde se ha investigado durante el desarrollo del presente estudio, no se ha podido hallar en la literatura disponible un valor específico de WTP para la detección de LMP en pacientes de alto riesgo CV sometidos a cirugía mayor no cardíaca. Ante esta carencia de datos específicos de WTP, se han analizado examinando la evolución de la curva CEAC, donde se ha considerado el valor de ICER como punto central del rango de la WTP.

3.2.7. Financiación del estudio

El estudio II ha sido financiado con una beca competitiva de investigación de la *Fundació La Marató de TV3* (expediente: 20150110), como uno de los subestudios del estudio I (ver apartado **3.1.9**.).

3.3. ESTUDIO III: Lesión miocárdica evaluada con imagen cardiaca avanzada tras cirugía mayor no cardiaca: un estudio piloto

3.3.1. Diseño del estudio

El estudio III se diseñó como un estudio piloto de casos y controles de cohorte, prospectivo, observacional y multicéntrico en el que se incluyeron los pacientes de dos hospitales terciarios de Barcelona: el Hospital de la Santa Creu i Sant Pau y el Hospital de Vall d'Hebrón.

3.3.2. Población del estudio y criterios de elegibilidad

El estudio III para el grupo de LMP incluyó pacientes con LMP diagnosticada (sin cumplir criterios de IM) mediante las mediciones de TncT-as, en los dos hospitales participantes que cumplían los siguientes criterios de inclusión:

1) Edad ≥65 años,

2) Deterioro preoperatorio de la función renal (FGe entre >30 y <60 mL/min/1,73 m^2) y,

3) Si la edad era <65 años, presentar antecedentes de AVC/AIT, o enfermedad vascular periférica.

Se excluyeron a los pacientes con historia de cardiopatía isquémica, ICC o contraindicación para la realización de las pruebas diagnósticas como la TCC o la RMC.

En el grupo de control se incluyeron pacientes del estudio I (exclusivamente del Hospital de la Santa Creu i Sant Pau) que no presentaron elevaciones de TncT-as postcirugía (apartado **3.1.2.**).

3.3.3. Metodología del estudio y procedimientos

Como se ha descrito anteriormente en el apartado **3.1.3.** del estudio I, a los pacientes incluidos en el estudio III se les realizaron tres mediciones de TncT-as: en el preoperatorio y a las 48 y 72 h después de la cirugía y la LMP se definió como un valor postoperatorio de TncT-as de ≥14 ng/L, con un aumento del ≥50% sobre el valor preoperatorio. A los pacientes con diagnóstico de LMP se les realizó un ECG y una ecocardiografía de control en el curso de la consulta cardiológica formal programada en el protocolo.

Estudios avanzados de imagen cardíaca (TCC y RMC)

A todos los pacientes incluidos en este estudio piloto se les practicó un TCC y una RMC durante el primer mes de alta hospitalaria. Ambas pruebas se realizaron en un único centro (Hospital de la Santa Creu i Sant Pau). En los días previos a la TCC, los pacientes recibieron tratamiento con un atenolol (25-50 mg) o ivabradina (5-7,5 mg) para lograr una FC ≤60 latidos por minuto. Dos evaluadores expertos, un cardiólogo y un radiólogo con formación de nivel 3 en interpretación de TCC, examinaron cada

angiografía sin conocer los datos clínicos, utilizando un modelo de 17 segmentos de las arterias coronarias. La gravedad anatómica por paciente se clasificó según el Sistema de Informes y Datos de Enfermedad de las Arterias Coronarias (*Coronary Artery Disease – Reporting and Data System - CAD-RADS*) (56). También se realizaron pruebas de TCC con triple descarte (enfermedad de las arterias coronarias, EP y patología aórtica aguda).

Posteriormente, se llevaron a cabo las pruebas de RMC para evaluar la contractilidad cardíaca global y segmentaria, así como la presencia de fibrosis focal, utilizando contraste con realce tardío de gadolinio (*late gadolinium enhancement - LGE*). El patrón de realce tardío de gadolinio se clasificó como "isquémico" cuando se observó realce sub-endocárdico o transmural en una distribución vascular, y como "no isquémico" si el realce se distribuía de forma parcheada o difusa, sin seguir un territorio vascular específico, principalmente en localizaciones mesocárdicas o epicárdicas (57).

Finalmente, a aquellos pacientes con EAC significativa identificada en la TCC (CAD-RADS ≥3), se realizó un estrés farmacológico con adenosina para evaluar el impacto funcional de cada estenosis coronaria.

3.3.4. Seguimiento de los pacientes

Todos los pacientes incluidos en el estudio III, tanto del grupo con LMP como del grupo control, recibieron un seguimiento durante los tres primeros días, así como al mes y al año después de la fecha de la cirugía, como el resto de los pacientes del estudio I, según se describe en el apartado **3.1.4.**

3.3.5. Variables del estudio

Las variables principales de este estudio fueron la prevalencia de EAC entre los pacientes con LMP y sin LMP y la incidencia de CCVM durante el seguimiento de 1 año. La variable compuesta de CCVM se definió según el protocolo del estudio I (apartado **3.1.6.**) incluyendo IM, ICC, nueva FA clínicamente relevante, AVC/AIT, EP o necesidad de revascularización cardíaca. También se registró la mortalidad por todas las causas.

Las variables secundarias fueron la incidencia al año de seguimiento de todos los componentes de la variable compuesta de CCVM, incluida la mortalidad por cualquier causa.

3.3.6. Análisis estadístico

Para las variables categóricas, se describieron los porcentajes y el número de casos, mientras que, para las variables cuantitativas, la media y desviación estándar o la mediana y el rango inter cuartil según la distribución de los datos. Las comparaciones entre grupos se llevaron a cabo mediante la prueba “t” de Student o la prueba “U” de Mann-Whitney, dependiendo de la naturaleza de las variables continuas, y con las pruebas de chi-cuadrado o la prueba exacta de Fisher para comparar proporciones de variables

categóricas. En todos los análisis, se aplicaron niveles de significaciones (p) bilaterales establecidos en 0,05. El procesamiento de los datos y los análisis estadísticos se llevaron a cabo utilizando STATA SE Versión 13.0 (StataCorp LLC, College Station, TX, EE. UU.).

3.3.7. Consideraciones éticas

Durante la hospitalización inicial, el equipo investigador identificó a los pacientes que cumplían los criterios de inclusión/exclusión y los invitó a participar en este estudio piloto de imagen cardíaca. El dictamen favorable específico para este estudio fue emitido por los Comités Éticos correspondientes de los dos hospitales participantes: Hospital de la Santa Creu i Sant Pau (11/05/16) y el Hospital de Vall d'Hebrón (5/11/2016). Todos los pacientes incluidos firmaron voluntariamente un consentimiento informado específico para el estudio de imagen, indicando su voluntad de participar en el mismo y en el seguimiento.

3.3.8. Financiación del estudio

El estudio III ha sido financiado con una beca competitiva de investigación de la *Fundació La Marató de TV3* (expediente: 20150110), como uno de los subestudios del estudio I (apartado **3.1.9**.), y por una beca competitiva de investigación del Instituto de Salud Carlos III y cofinanciada por el Fondo Europeo de Desarrollo Regional "Una manera de hacer Europa" (expediente: PI16/01162), otorgada a E. Popova como Investigador Principal.

4. RESULTADOS

4. RESULTADOS

Los resultados de la tesis se presentan de acuerdo con los estudios correspondientes que la conforman, los cuales han dado lugar a la publicación de los tres artículos que se presentan a continuación:

4.1. ESTUDIO I. Importancia de la implementación del cribado sistemático del daño miocárdico perioperatorio en pacientes de cirugía no cardiaca

Título	**The relevance of implementing the systematic screening of perioperative myocardial injury in noncardiac surgery patients**
Referencia	Popova E, Paniagua-Iglesias P, Álvarez-García J, Vives-Borrás M, González-Osuna A, García-Osuna A, Rivas-Lasarte M, Hermenegildo-Chávez G, Diaz-Jover R, Azparren-Cabezón G, Barceló-Trías M, Moustafa AH, Aguilar-López R, Ordóñez-Llanos J, Alonso-Coello P. J Clin Med. 2023 Aug 18;12(16):5371. DOI: 10.3390/jcm12165371. PMID: 37629413; PMCID: PMC10455326.
Factor de impacto y cuartil	3,9
Cuartil	Q 2
Categoría	Medicine, General & Internal

4.1.1. Resumen de resultados del estudio I

- *Población del estudio*

Durante el periodo de estudio, en el Hospital Santa Creu i Sant Pau fueron operados de una cirugía mayor no cardiaca un total de 2333 pacientes elegibles; de los mismos, 568 (24,3%) no pudieron incluirse por haber sido intervenidos durante el fin de semana o días festivos y 187 (8,01%) por no haber sido identificados en el tiempo establecido en el protocolo. De los 1578 pacientes elegibles restantes, 68 pacientes (4,30%) rechazaron la inclusión, mientras que 33 (2,09%) aceptaron participar inicialmente, pero solicitaron su retirada del estudio posteriormente. A lo largo del seguimiento postoperatorio, que se prolongó hasta marzo de 2020, solo se perdió el seguimiento de un solo paciente (y no por fallecimiento) por lo que fue excluido. Finalmente, se incluyeron 1477 pacientes con seguimiento completo.

- *Proceso de implementación del cribado sistemático*

El proceso de implementación del cribado sistemático con TncT-as se llevó a cabo por el equipo multidisciplinario. La información sobre el inicio del estudio se difundió entre los servicios participantes a través de reuniones informativas; los profesionales informados mostraron una buena aceptación del protocolo del estudio. La información a los profesionales recalcó la necesidad de maximizar las solicitudes de mediciones preoperatorias de TncT-as en las plantillas de evaluación anestésica/prequirúrgica para pacientes de alto riesgo, garantizando la obtención de todas las mediciones preoperatorias. Se propuso informatizar la solicitud de TncT-as postoperatorias y las consultas cardiológicas en caso de elevación de dicho marcador; sin embargo, el departamento de informática no pudo satisfacer dicha petición, y fue necesario realizarlas de forma manual. Las mediciones de TncT-as en el postoperatorio se completaron en el 89,5% de los casos; mientras que en el 10,5% restante se perdió la medida de TncT-as a las 72 horas por altas hospitalarias precoces. En caso de LMP detectada, se llegó a realizar ECG postoperatorios de control en el 65,1%, y la consulta de cardiología formal y el ecocardiograma en el 56,9%. El seguimiento a 1 mes y 1 año se completó con éxito en el 99,9%, gracias al soporte continuo del equipo investigador.

- *Incidencia de LMP y características de los pacientes*

En los 1477 casos de la cohorte de estudio, el 94,8% fueron mayores de 65 años y el 57,2% mujeres. La LMP se diagnosticó en 232 pacientes, con una prevalencia del 15,7% (IC del 95%: 13,9-17,6%). Los pacientes con LMP presentaron comorbilidades preoperatorias más frecuentemente que aquellos sin LMP: IM (17,7% vs. 11,6%; p=0,014), ICC (15,1% vs. 6,4%; p<0,001), FA (24,1% vs. 13,4%; p<0,001), AVC/AIT (14,6% vs. 8,4%; p=0,005), HTA (80,6% vs. 69,2%; p<0,001), DM (31,0% vs. 23,5%; p=0,017) y deterioro de la función renal (31,2% vs. 15,7%; p<0,001). En consecuencia, los pacientes con LMP presentaron un mayor IRCR, clasificado como III-IV que los pacientes sin LMP (17,7% en los casos de LMP vs. 10,3% en los casos sin LMP). Además, los pacientes con LMP también presentaron preoperatoriamente valores significativamente inferiores de FGe, (p<0,001) y Hb (p<0,001) o superiores de TncT-as (p<0,001).

Durante la cirugía, así como en el postoperatorio inmediato, los pacientes con LMP experimentaron una mayor incidencia de inestabilidad hemodinámica y sangrado postoperatorio en comparación con los pacientes sin LMP. Las diferencias más notables incluyeron mayor incidencia de hipotensión significativa (37,3% vs. 29,0%, p=0,014), de hipotensión que requirió tratamiento con fármacos vasopresores (26,1% vs. 15,9%; p=0,026), de taquicardia significativa (30,0% vs. 18,3%; p <0,001), de sangrado postoperatorio (17,3% vs. 8,1%; p<0,001) o de shock postoperatorio (6,3% vs. 2,5%; p=0,008).

- *Resultados de seguimiento*

En toda la cohorte, durante el primer mes de seguimiento la mortalidad por cualquier causa ocurrió en 25 pacientes (1,7% del total, IC del 95%: 1,1-2,4%). Al cumplirse el año de seguimiento, la mortalidad por cualquier causa fue de 104 pacientes (7,0%; p<0,001 respecto al primer mes). Las muertes atribuidas a causas CV también aumentaron con el tiempo desde el 0,9% en el primer mes hasta el 2,1% al año del seguimiento (p=0,01).

En el primer mes de seguimiento, tanto la mortalidad por cualquier causa (1,7%) como la de causa CV (0,9%) fue la misma en los pacientes con LMP y sin LMP. Sin embargo, en el seguimiento de un año, los pacientes con LMP presentaron tasas significativamente superiores de mortalidad por todas las causas (11,2%) a la de aquellos sin LMP (6,3%, p<0,001 vs. LMP). También se observó mayor mortalidad CV al año de seguimiento en los casos con LMP (3,9%) que en los casos LMP (1,8%), aunque en este caso la diferencia entre % no alcanzó significación estadística.

Los componentes individuales de CCVM, excepto el IM, que fue más frecuente entre los pacientes con LMP en el primer mes (3,0% vs. 0,3% en casos sin LMP, p<0,001), se observaron con mayor frecuencia en el seguimiento hasta un año. En el seguimiento a largo plazo, los pacientes con LMP presentaron más casos de ICC (6,0% vs. 2,6%, p=0,011) y los únicos pacientes que requirieron revascularización cardiaca fueron aquellos afectos de LMP (1,4% vs. 0%, p=0,001) que además cumplieron con criterios de IM.

Tomando en conjunto todos los anteriores datos, la frecuencia de CCVM fue significativamente superior en pacientes con LMP en el primer mes de seguimiento (9,5% vs. 3,6% en no LMP; p<0,001) y al año de este (8,6% vs. 4,3%, p=0,009).

La infección postoperatoria, fue la complicación más frecuente entre todas las existentes durante el primer mes de seguimiento. Se registró en el 15,5% de toda la cohorte, disminuyendo significativamente en los meses posteriores hasta el 7,7%, al año del seguimiento (p<0,02). Los pacientes con LMP tenían tasas significativamente más altas de infección que aquellos sin LMP en el seguimiento de primer mes (23,3% vs. 14,5%, p=0,001). Sin embargo, las tasas de infección al año de seguimiento disminuyeron hasta el 10,5% en los casos de LMP y el 7,1% en aquellos sin LMP, sin que existieran diferencias significativas entre ambos grupos.

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The Relevance of Implementing the Systematic Screening of Perioperative Myocardial Injury in Noncardiac Surgery Patients

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Abstract: Perioperative myocardial injury (PMI) is a common cardiac complication. Recent guidelines recommend its systematic screening using high-sensitivity cardiac troponin (hs-cTn). However, there is limited evidence of local screening programs. We conducted a prospective, single-center study aimed at assessing the feasibility and outcomes of implementing systematic PMI screening. Hs-cTn concentrations were measured before and after surgery. PMI was defined as a postoperative hs-cTnT of ≥14 ng/L, exceeding the preoperative value by 50%. All patients were followed-up during the hospitalization, at one month and one year after surgery. The primary outcome was the incidence of death and major cardiovascular and cerebrovascular events (MACCE). The secondary outcomes focused on the individual components of MACCE. We included two-thirds of all eligible high-risk patients and achieved almost complete compliance with follow-ups. The prevalence of PMI was 15.7%, suggesting a higher presence of cardiovascular (CV) antecedents, increased perioperative CV complications, and higher preoperative hs-cTnT values. The all-cause death rate was 1.7% in the first month, increasing up to 11.2% at one year. The incidence of MACCE was 9.5% and 8.6% at the same time points. Given the observed elevated frequencies of PMI and MACCE, implementing systematic PMI screening is recommendable, particularly in patients with increased cardiovascular risk. However, it is important to acknowledge that achieving optimal screening implementation comes with various challenges and complexities.

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1. Introduction

Perioperative myocardial injury (PMI) in noncardiac surgery is a frequent cardiac complication strongly associated with an increased rate of death and morbidities [1,2]. Eight million patients will experience a PMI, and one million will die within 30 days after surgery out of the 300 million yearly surgical procedures performed worldwide [3,4]. PMI is often missed because it can be clinically silent in more than 80% of cases; some PMI-alerting symptoms, like chest pain, are often masked or suppressed by postoperative sedation and analgesia [2,5]. Therefore, it is recommended to systematically measure a cardiac-specific biomarker, such as troponin (cTn), to facilitate the timely detection of PMI, particularly in patients with high cardiovascular risk [1–5]. Existing evidence emphasizes the importance of measuring cTn levels both before and after surgery, as this allows differentiation between acute cTn concentration increases associated with PMI and chronic elevations caused by other factors [1,5]. Moreover, the use of a high-sensitivity cTn (hs-cTn) assay enhances the early and sensitive detection of even minor instances of PMI [6,7].

In recent years, several national and international guidelines [8–14] have issued recommendations for the systematic screening of PMI using hs-cTn, instead of relying only on clinical symptoms. Despite the demonstrated efficiency and cost-effectiveness of systematic PMI screening with hs-cTn [15], especially for high cardiovascular risk patients undergoing major surgeries [16], its implementation is still limited in clinical practice. Consequently, there is scarce evidence derived from local practices regarding the implementation of systematic hs-cTnT screening programs. This situation may be attributed to a lack of established diagnostic criteria, limited available data on management strategies, and the uncertainty surrounding the impact of screening on patients, all of them important outcomes in real-world scenarios [2,17,18].

Given the growing importance of the early detection of perioperative PMI, we conducted a prospective cohort study to evaluate the feasibility and impact of implementing systematic PMI screening, which included measuring hs-cTn levels before and after surgery in high-risk noncardiac surgery patients. In this work, we present the clinical results and discuss the challenges and complexities encountered during the implementation process of the screening program at our institution.

2. Materials and Methods

2.1. Study Characteristics

2.1.1. Study Site and Design

Our study was conducted at a single university tertiary hospital. It was an observational prospective study aimed at implementing systematic hs-cTnT screening in high-risk patients who underwent scheduled or urgent noncardiac surgery [19]. The choice of the biomarker to be measured was based on bibliographic antecedents [3–7] and on the previous experience of our researchers, who had participated in previous studies that used troponins as cardiac biomarkers [3,20]. Additionally, the criteria for conducting serial analysis and identifying abnormal values and patterns were drawn from studies evaluating hs-cTnT in daily practice and recommendations regarding its use for detecting myocardial injury [21–24]. Our hospital started measuring hs-cTnT, although as clinical practice tool (not for systematic screening) already in November 2009.

2.1.2. Time of the Study

Our study was conducted between July 2016 and March 2019 and was registered at Clinicaltrials.gov (NCT03438448). We followed the STROBE reporting guidelines to ensure transparent reporting of our findings (Supplementary Table S1).

2.1.3. Ethics and Patient Recruitment

Ethical approval for the study was provided by the Ethical Committee of Clinical Investigation at Hospital de la Santa Creu i Sant Pau, Barcelona (Spain). The approval, identified by the unique Protocol ID: IIBSP-IMP-2015-95, was issued on 11 May 2016. The study was conducted in accordance with the principles set forth in the Declaration of Helsinki.

The identification of eligible patients was carried out during the preoperative assessments by members of the research team. Prior to enrolment, all potentially eligible patients were informed about the study protocol and provided with detailed information. They voluntarily signed written informed consent, indicating their willingness to participate in the study after surgery and before hospital discharge.

2.1.4. The Research Team and hs-cTnT Screening Implementation Management

Our study protocol was designed and accomplished by a newly formed, multidisciplinary research team that included investigators from the departments of Anesthesiology, Cardiology, Clinical Biochemistry, Clinical Epidemiology, and Surgery. They all worked together to supervise the execution of the protocol, evaluate the results, and identify any barriers that impeded its implementation.

2.1.5. Data Collection and Management

During the hospitalization period, our research team performed daily reviews of the clinical records and charts of all enrolled patients until their discharge. This systematic process enabled the comprehensive and real-time collection of information pertaining to the patient's medical condition and progress. In the one-month and one-year follow-up evaluations, patients or their family members were interviewed by phone to obtain information regarding the occurrence of the main outcomes of interest. If any such events were reported, the research personnel obtained pertinent source documents to validate and document the specific details. To facilitate data collection and management, an electronic case report form (eCRF) was created. This eCRF was designed in a secure online database (www.clinapsis.com), accessed on 1 May 2016, ensuring the confidentiality and integrity of the collected data.

2.2. Study Population

We included high-risk cardiovascular patients in our study. Inclusion criteria comprised aged $\geq$ 65 years or, if younger, had at least one documented antecedent of cardiovascular diseases (e.g., coronary artery disease, chronic heart failure, stroke, transient ischemic attack, or peripheral vascular disease) or impaired renal function (estimated glomerular filtration rate < 60 mL/min/1.73 m^2). These patients underwent elective or urgent major noncardiac surgeries, including orthopedic, traumatological, spinal, visceral, digestive, peripheral vascular, thoracic, gynecologic, plastic, or otorhinolaryngologic procedures, and required at least an overnight hospital stay. We excluded patients aged < 65 years without cardiovascular diseases, those undergoing minor surgeries, and those operated on during weekends and holidays. Patients unable to comprehend the protocol and/or sign the informed consent were also excluded.

2.2.1. Cardiac Biomarker Measurements

Hs-cTnT measurements were performed at three specific time points: preoperatively (at the preoperative visit or just before surgery) and at 48 and 72 h after surgery. For elective surgeries, the preoperative hs-cTnT measurements were requested by the surgeons and/or anesthesiologists conducting the preoperative visits. In the case of urgent, non-elective surgeries, the measurements were either requested by surgeons or anesthesiologists in charge or determined from plasma aliquots stored at 4 °C in the clinical laboratory for not longer than 24 h. The postoperative hs-cTnT measurements were requested by the attending physicians at recovery units, with support from the Clinical Epidemiology department.

Hs-cTnT was measured by an electrochemiluminescent immune assay (Roche Diagnostics, Basel, Switzerland) with a measuring range of 5.0–10,000 ng/L, a limit of detection 5.0 ng/L, a 99th upper reference percentile (URL) of 14 ng/L, and 13 ng/L at the 10% coefficient of variation.

2.2.2. PMI Definition, Diagnostic, and Management

The combination of pre- and postoperative hs-cTnT measurements was employed to differentiate between acute and chronic hs-cTnT elevations and to identify any pre-existing myocardial injury related to the surgery at an earlier stage [1]. The criteria for PMI were established based on a bibliography [25] and considering the prior experience of our research team. PMI was defined as a postoperative hs-cTnT concentration of ≥14 ng/L, along with an increase of ≥50% from the preoperative value. For myocardial infarction (MI), we followed the guidelines provided by the third universal definition [26], as our protocol was developed in the year 2016.

When PMI was identified, a formal cardiology evaluation was conducted, which included a thorough examination of all available clinical records, a 12-lead electrocardiogram (ECG), and an echocardiogram to detect any new regional wall motion abnormalities. PMI was ruled out when the elevated levels of hs-cTnT were determined by the cardiologists to be caused by noncardiac and/or non-ischemic factors such as sepsis, pulmonary embolism, or electrical cardioversion. Cardiologists, in collaboration with attending physicians, reviewed and assessed the use of medications such as aspirin, other antiplatelets, angiotensin-converting enzyme inhibitors (ACEI)s, statins, beta-blockers, and oral anticoagulants. Additionally, they evaluated the necessity for further diagnostic procedures, such as coronary angiography, and determined the potential need for coronary revascularization if deemed appropriate.

2.2.3. Follow-Up

All the included patients underwent follow-up assessments during their initial hospitalization period, as well as one month and one year after surgery. We considered the assessment conducted within the first three days following surgery as the immediate postoperative assessment. Following the discharge, a personalized follow-up plan was recommended for some PMI patients based on their individual characteristics, involving either the hospital or primary care specialists responsible for the patients' ongoing care. The discharge report included further details regarding the diagnosis of PMI (or MI) and provided recommendations for their appropriate management.

The follow-up evaluations at one month and one year following the initial surgery were performed by the research personnel. These assessments involved conducting phone interviews with the patients directly or with their close relatives. Additionally, electronic clinical records were reviewed to collect relevant information regarding outcome events and their associated specifics. The detailed descriptions of our screening program are shown in Figure 1.

2.3. Outcomes

Our primary outcome was to assess the incidence of death and major cardiovascular and cerebrovascular events (MACCE) within one month and one year after surgery. All-cause death was defined as any death attributed to a clearly documented non-vascular cause, while cardiovascular death was defined as any death attributed to cardiovascular or unknown causes. MACCE was defined as the composite outcome of major adverse cardiac and cerebrovascular events: myocardial infarction, congestive heart failure, new clinically relevant atrial fibrillation, stroke (including transient ischemic attack (TIA)), pulmonary embolism, and the need for cardiac revascularization. The definitions of these individual components were based on the guidelines in effect during the study period. The secondary outcomes were focused on the individual components of MACCE to allow for the analysis and understanding of the impact of each cardiovascular event on the overall outcome.

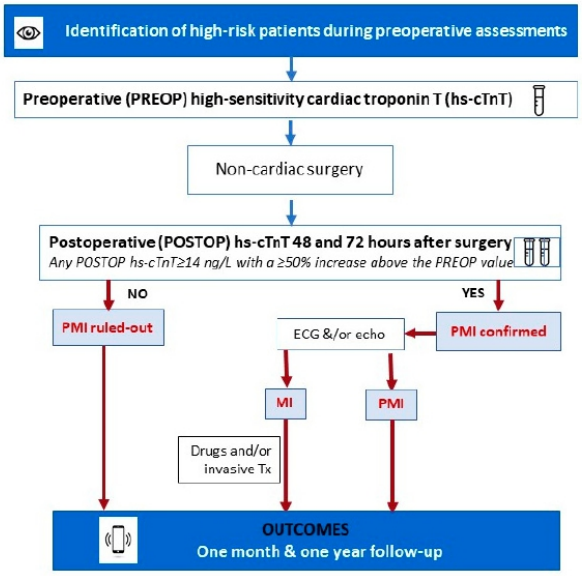

Figure 1. Systematic PMI screening with hs-cTnT.

2.4. Statistical Analysis

Variables were presented as the percentage and number of cases for categorical variables or mean and standard deviation for quantitative ones; exceptions to this presentation are specifically mentioned in the Tables. Inferential statistics were employed to analyze the data and determine statistical significance. The prevalence and/or incidence of outcomes were reported along with their corresponding 95% confidence intervals. To assess the univariate associations between independent variables and the primary outcomes (death and MACCE), we employed various statistical tests such as chi-square test, Fisher's exact test, *t*-tests, or non-parametric tests depending on the nature of the variable.

3. Results

During the study period, a total of 2333 eligible patients underwent surgery at our hospital. Out of these, 568 patients (24.3%) were excluded as they underwent surgery on weekends or holidays; 187 patients (8.01%) were not included due to a delay in their identification. Sixty-eight (2.91%) patients declined to participate, while 33 (1.41%) patients who initially agreed to participate later requested to withdraw from the study. Throughout the postoperative follow-up, which extended until March 2020, only one of the included surviving patients was lost to follow-up. The recruitment flowchart is shown in

3.1. Hs-cTnT Screening Implementation Management

Our multidisciplinary research team worked together to implement hs-cTnT screening in the tertiary hospital, showing the local experience as a real example for other sites. The information regarding our ongoing study has been effectively disseminated among the participating surgical departments in our center through informative meetings. Health professionals have shown great acceptance of the study protocol, even though we did not gather feedback through surveys or interviews. We have successfully integrated the request for preoperative hs-cTnT measurements into the anesthetic assessment templates for high-risk patients. Regrettably, due to the lack of support from the IT Department, we were compelled to manually request blood samplings, formal cardiology evaluations, and follow-up visit reminders. However, this manual approach proved to be insufficient for implementing systematic hs-cTnT screening into our routine clinical practice. Figure 2.

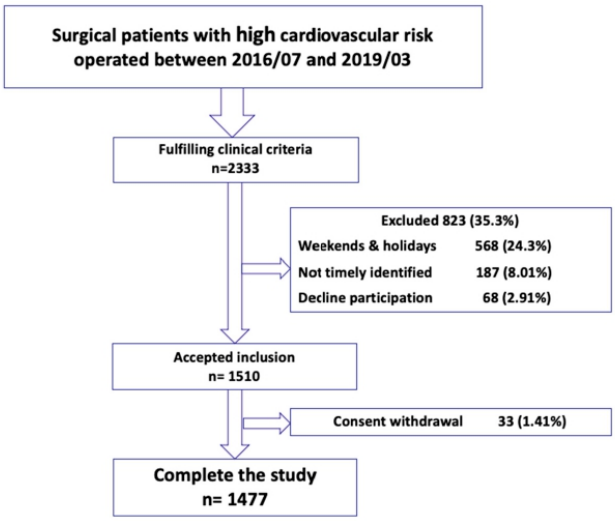

Figure 2. Recruitment flowchart.

3.1.1. Cardiac Biomarker Availability at Recruitment

In elective surgeries, preoperative hs-cTnT measurements were predominantly obtained during the month preceding the scheduled surgery, coinciding with the time of the decision for the intervention (68% of cases). In the remaining cases, preoperative samples for hs-cTnT were collected within the six months prior to surgery (30% of cases), and in a small percentage of cases (2% of cases), the preoperative samples were collected more than six months before the surgery. In contrast, for urgent surgeries, preoperative hs-cTnT measurements were obtained just a few minutes before the surgery.

3.1.2. PMI Incidence, Clinical Data of Patients

In our cohort, PMI was observed in 232 patients, indicating a prevalence of 15.7% (95% CI 13.9–17.6) among the 1477 patients included in the study. The baseline characteristics of the 1477 patients are presented in Table 1, both as a group and stratified based on the presence or absence of PMI. No significant differences were observed in the occurrence of PMI based on age or sex. Most patients (94.8%) were included in the study due to being aged 65 years or older, and slightly over half of them were women (57.2%).

Compared to patients without PMI, those with PMI had a higher prevalence of preoperative comorbidities, which included: previous myocardial infarction (17.7% vs. 11.6%; $p = 0.014$), congestive heart failure (15.1% vs. 6.4%; $p < 0.001$), atrial fibrillation (24.1% vs. 13.4%; $p < 0.001$), stroke/transient ischemic attack (14.6% vs. 8.4%; $p = 0.005$), arterial hypertension (80.6% vs. 69.2%; $p < 0.001$), diabetes mellitus (31.0% vs. 23.5%; $p = 0.017$), and impaired renal function (31.2% vs. 15.7%; $p < 0.001$). Consequently, PMI patients more frequently had higher Revised Cardiac Risk Indexes (III–IV) than those without PMI (17.7% vs. 10.3%). Additionally, PMI patients also presented significantly worse values of certain baseline laboratory variables, such as lower estimated glomerular filtration rate ($p < 0.001$) and hemoglobin concentration ($p < 0.001$) and higher preoperative hs-cTnT value ($p < 0.001$).

Table 1. Baseline characteristics of the study population according to the presence (PMI) or absence (No PMI) of perioperative myocardial injury after surgery.

Baseline Characteristics	All Patients % (*N* 1477)	PMI % (*N* 232)	No PMI % (*N* 1245)	*p*-Value
Age ≥ 65 years	94.8 (1399)	96.1 (223)	94.5 (1176)	NS
Women	57.2 (843)	58.2 (135)	57.1 (708)	NS
Antecedents at the preoperative visit				
Myocardial infarction	12.5 (185)	17.7 (41)	11.6 (144)	0.014
Congestive heart failure	7.7 (114)	15.1 (35)	6.4 (79)	<0.001
Atrial fibrillation	15.1 (223)	24.1 (56)	13.4 (167)	<0.001
Stroke/TIA	9.4 (139)	14.6 (34)	8.4 (80)	0.005
Pulmonary embolism	1.4 (21)	0.4 (1)	1.6 (20)	NS
Deep vein thrombosis	2.0 (30)	2.2 (5)	2.0 (25)	NS
Peripheral artery disease	10.4 (153)	13.8 (32)	9.7 (121)	NS
Arterial hypertension	71.0 (1048)	80.6 (187)	69.2 (861)	<0.001
Diabetes mellitus	24.7 (364)	31.0 (72)	23.5 (292)	0.017
Dyslipidemia	50.9 (751)	55.2 (128)	50.1 (623)	NS
COPD	13.6 (200)	11.6 (27)	13.9 (173)	NS
Impaired renal function	18.1 (267)	31.2 (72)	15.7 (195)	<0.001
Revised Cardiac Risk Lee Index				
I	56.2 (828)	47.2 (109)	57.9 (719)	0.003
II	32.4 (477)	35.1 (81)	31.9 (396)	
III	8.1 (120)	13.4 (31)	7.2 (89)	
IV	3.3 (48)	4.3 (10)	3.1 (38)	
eGFR (mL/min/1.73 m^2)				
≤30	5.0 (72)	7.1 (16)	4.6 (56)	<0.001
31–59	21.0 (305)	31.6 (71)	19.1 (234)	
≥60	74.0 (1075)	61.3 (138)	76.4 (937)	
Preoperative hemoglobin (g/L)				
≤100	10.7 (157)	16.5 (38)	9.6 (119)	<0.001
101–129	38.9 (572)	44.2 (102)	37.9 (470)	
≥130	50.5 (743)	39.4 (91)	52.5 (652)	
Preoperative hs-cTnT (ng/L) *	13 (9–22)	15 (11–26)	13 (9–21)	<0.001

* Hs-cTnT as median (interquartile range). Abbreviations: NS—Not significant: PMI—perioperative myocardial injury; TIA—transient ischemic attack; COPD—chronic obstructive pulmonary disease; eGFR—estimated glomerular filtration rate (using the CKD-EPI formula); Hs-cTnT—cardiac troponin T measured with a high-sensitivity method.

3.1.3. Immediate Postoperative Assessment

A total of 155 (10.5%) postoperative hs-cTnT measurements were not recorded in patients who were discharged before the three-day mark after the intervention or during weekends. This was attributed to attending physicians being unaware of the study protocol. Similarly, as in the case of preoperative values, hs-cTnT concentrations were observed to be significantly higher (2 to 2.5-fold) in patients with PMI compared to patients without PMI at both 48 and 72 h after surgery ($p < 0.001$ for both comparisons). Among the 232 patients with PMI, a postoperative ECG was obtained in 151 patients (65.1%), and formal cardiology consultation was conducted in 132 patients (56.9%). Additionally, all 132 patients who received cardiology consultation underwent an additional echocardiogram. Most PMI patients in our cohort (220; 94.8%) were asymptomatic.

New or presumed new changes in ECG were observed in 6.0% (9 out of 151) of the postoperative ECGs, and presumed new echocardiographic wall motion abnormalities in

11.4% (15 out of 132) of the performed echocardiographic tests. Thus, only 3.0% (7 out of 232) of the PMI patients met the criteria for myocardial infarction according to the existing international definitions. PMI patients experienced a higher incidence of hemodynamic instability and bleeding compared to non-PMI patients. The most notable differences included a higher occurrence of significant hypotension (37.3% vs. 29.0%, $p = 0.014$) requiring vasopressor drugs (26.1% vs. 15.9%; $p = 0.026$), significant tachycardia (30.0% vs. 18.3%; $p < 0.001$), immediate postoperative bleeding (17.3% vs. 8.1%; $p < 0.001$), and postoperative shock (6.3% vs. 2.5%; $p = 0.008$) (Table 2).

Table 2. Surgery characteristics and intra- and immediate postoperative clinical complications.

	All Patients % (*N* 1477)	PMI % (*N* 232)	No PMI % (*N* 1245)	*p*-Value
Priority of surgery				
Elective	71.6 (1054)	58.9 (136)	74.0 (918)	<0.001
Urgent	28.4 (418)	41.1 (95)	26.0 (323)	
	INTRAOPERATIVE Complications			***p*-Value**
Significant arterial hypotension	71.8 (1043)	77.2 (176)	70.8 (867)	0.044
Requiring treatment	59.0 (619)	70.3 (123)	56.8 (496)	0.001
Significant arterial hypertension	43.5 (637)	44.8 (103)	43.2 (534)	NS
Requiring treatment	10.6 (67)	9.8 (10)	10.8 (57)	NS
Significant tachycardia	9.3 (135)	12.3 (28)	8.7 (107)	NS
Requiring treatment	8.2 (12)	16.7 (5)	6.0 (7)	NS
Significant bradycardia	32.2 (470)	32.3 (74)	32.2 (396)	NS
Requiring treatment	10.3 (48)	13.9 (10)	9.7 (38)	NS
Bleeding	4.0 (59)	7.8 (18)	3.3 (41)	0.004
Shock	3.9 (57)	8.2 (19)	3.1 (38)	0.001
Hypovolemic	96.4 (54)	94.4 (17)	97.4 (37)	NS
Distributive	3.6 (2)	5.6 (1)	2.6 (1)	NS
Significant hypoxemia (SaO_2 < 90%)	2.0 (30)	2.6 (6)	1.9 (24)	NS
	Immediate POSTOPERATIVE Complications (in the First 3 Postoperative Days)			***p*-Value**
Significant arterial hypotension	30.3 (438)	37.3 (85)	29.0 (353)	0.014
Requiring treatment	17.8 (87)	26.1 (24)	15.9 (63)	0.026
Significant arterial hypertension	58.5 (848)	54.1 (124)	59.3 (724)	NS
Requiring treatment	7.0 (59)	8.1 (10)	6.8 (49)	NS
Significant tachycardia	20.0 (291)	30.0 (68)	18.3 (223)	<0.001
Requiring treatment	5.7 (17)	9.0 (6)	4.8 (11)	NS
Significant bradycardia	37.9 (547)	31.9 (73)	38.1 (474)	0.04
Requiring treatment	1.7 (9)	0.0 (0)	2.0 (9)	0.105
Bleeding	9.6 (139)	17.3 (40)	8.1 (99)	<0.001
Shock	3.1 (45)	6.3 (14)	2.5 (31)	0.008
Hypovolemic	93.5 (43)	100.0 (14)	90.6 (29)	NS
Distributive	4.3 (2)	0.0 (0)	6.3 (2)	NS
Septic	2.2 (1)	0.0 (0)	3.1 (1)	NS
Significant hypoxemia (SaO_2 < 90%)	15.2 (218)	18.5 (41)	14.6 (177)	NS
Postoperative hs-cTnT (ng/L) *				
48 h	16 (10–27)	32 (20–56)	14 (9–22)	<0.001
72 h	14 (9–24)	30 (17–52)	13 (8–20)	<0.001

* Hs-cTnT as median (interquartile range). Abbreviations: NS—Not significant: PMI—perioperative myocardial injury; Hs-cTnT—cardiac troponin T measured with a high-sensitivity method. Definitions: Significant hypotension: drop of 30% of arterial systolic blood pressure (SBP) from baseline (before anesthetic induction); significant hypertension: SBP > 140 mmHg and/or diastolic blood pressure (DBP) > 90 mmHg; significant tachycardia: heart rate (HR) > 100 beats per minute (bpm); significant bradycardia: HR < 60 bpm; bleeding: postoperative hemoglobin (Hb) concentration < 70 g/L + need of transfusion of 2 pools or Hb drop of >50 g/L from preoperative value or transfusion of >3 (FBC) within 24 h; significant hypoxemia—oxygen saturation (SaO_2) < 90%.

3.2. Follow-Up and Outcomes

We achieved a significantly high level of compliance with telephone follow-ups conducted by our research team. The compliance rate was 99.9% at both the one-month and one-year marks. As shown in Figure 3 (Supplemental Table S4), in the whole cohort, infection was the most common outcome at one month after surgery, occurring in 15.9% of patients. However, the rate of infection decreased significantly in the subsequent months (7.7%, $p = 0.02$). On the other hand, all the MACCE and its individual components, except for new atrial fibrillation or myocardial infarction, were more frequently observed in the months following the first month after surgery. During the first month, a total of 25 all-cause deaths occurred, accounting for 1.7% (95% CI: 1.1–2.4%) of the entire cohort. In the following months, there was a significant increase in all-cause deaths, with a total of 104 deaths (7.0% of the survivors, $p < 0.001$ compared to the first month). Among these deaths, those attributed to cardiovascular causes also increased over time. The rate of cardiovascular deaths in the whole cohort was 0.9% in the first month and increased to 2.1% among survivors in the subsequent months ($p = 0.010$).

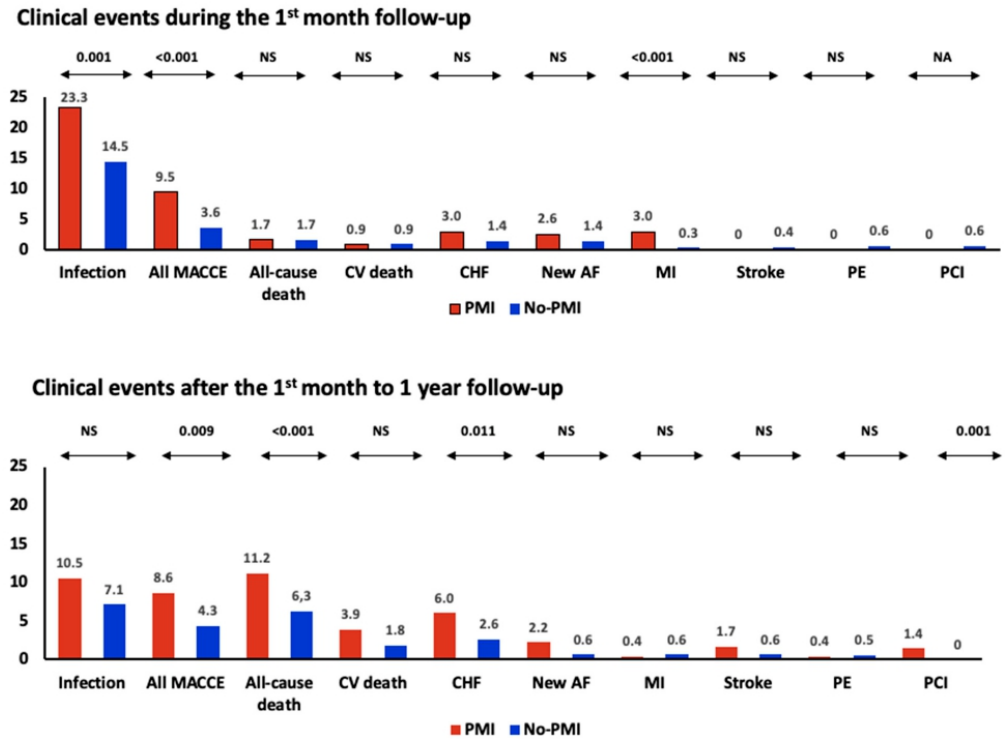

Figure 3. Percentages of clinical events observed in the earlier (first month, 1st-m) and subsequent (first month to one year, 1 y) follow-up periods. p-values are for comparison between respective follow-up periods in each subgroup (PMI, No-PMI) of patients. Abbreviations: NS—Not significant: MACCE—Major adverse cardiovascular and cerebrovascular events; CHF—congestive heart failure; AF—atrial fibrillation; MI—myocardial infarction; PE—pulmonary embolism; PCI—percutaneous coronary intervention. Definitions: All-cause death—any death attributed to a clearly documented non-vascular cause. Cardiovascular death—any death attributed to cardiovascular or unknown causes.

At the one-month follow-up, we observed that PMI patients had significantly higher rates of infection (23.3% vs. 14.5%, $p = 0.001$), all MACCE (9.5% vs. 3.6%, $p < 0.001$), and myocardial infarction (3.0% vs. 0.3%, $p < 0.001$) compared to patients without PMI. These outcomes (infection, all MACCE, and MI) were the only ones that exhibited significant differences between the two groups of PMI and no-PMI patients. The all-cause death rate in PMI patients was 1.7% in the first month after surgery, which increased to 11.2% at one year. It is important to note that at one month, no significant differences were observed between patients with PMI and those without PMI in terms of all-cause or cardiovascular deaths. However, in the subsequent months up to one year, these differences became more notable with a higher percentage of deaths in the PMI group (11.2% vs.6.3%, $p < 0.001$). Additionally, the occurrence of congestive heart failure (6.0% vs. 2.6%, $p = 0.001$) and the need for coronary revascularization (1.4% vs. 0%, $p = 0.001$) were significantly higher in the PMI group. This indicates a distinct pattern of increasing cardiovascular outcomes beyond the initial month following surgery. Taken together, these results indicate that PMI patients experienced a high incidence of MACCE throughout the entire follow-up period. During the first month follow-up, both MI and congestive heart failure (CHF) occurred with similar frequency in PMI patients. However, in the subsequent months, there was a predominance of CHF as compared to MI. This suggests that the occurrence of CHF becomes more prominent as time progresses following PMI.

3.3. Cardiovascular Drugs Use Pre and Postintervention

In our cohort, cardioactive drugs were more frequently used in PMI patients compared to those without PMI, both before and after surgery, except for statins and antiplatelets. The percentage of PMI patients receiving aspirin (AAS), other antiplatelets, beta-blockers, ACEIs, and oral anticoagulants was significantly higher than in no-PMI patients at baseline (p-values ranging from 0.003 to 0.009), at the first month after the intervention (p-values ranging from 0.032 to 0.001), and during the period between the first and subsequent months of the postoperative period (p-values ranging from 0.006 to 0.001). Among these drugs, angiotensin-converting enzyme inhibitors were the most prescribed. Importantly, the percentage of prescribed drugs did not differ significantly between PMI and no-PMI patients throughout the postoperative period (Supplemental Table S2).

4. Discussion

Recent international guidelines recommend [14] or suggest [27] implementing systematic PMI screening with hs-cTnT in high-risk patients undergoing noncardiac surgery. However, there is still limited experience of such implementation in local practice [2,17,18]. Our cohort study proves the effectiveness of systematic hs-cTnT screening for high-risk patients at a university hospital, revealing a high PMI prevalence, especially in patients with a history of cardiovascular risk factors (CVRF) or cardiovascular disease (CVD). PMI was associated with intraoperative or immediate postoperative complications such as hypotension, bleeding, or arrhythmias. Furthermore, during the follow-up period, PMI patients had higher rates of mortality and major cardiovascular adverse events. These observations pointed out the need for and usefulness of implementing systematic PMI screenings in high-risk patients and aligned with recent ESC guidelines [14], despite being issued five years after our study began. This accomplishment stems from the expertise and prior experience of our research team, actively participating in generating evidence on the study topic [3,20,22,23]. Although developed in 2016, our approach remains in line with ESAIC's more cautious recommendations in 2023 [27].

4.1. Screening Implementation. Barriers and Facilitators

Despite some challenges and barriers, our dedicated research team successfully recruited two-thirds of all eligible high-risk patients and followed them for up to one year. The exclusion of weekend and holiday surgeries, primarily due to personnel unavailability, resulted in the loss of 24.3% of eligible cases. For the same reason, an additional 8.01%

of cases were lost by delayed identification. In contrast, a minimal number of patients declined to participate, either before or after inclusion. Despite lacking the IT Department's assistance to ensure automated requests, we were able to obtain extensive clinical data during pre, peri, and immediate postoperative steps. We achieved successful one-month and one-year follow-ups for all but one participant.

Analyzing barriers and facilitators, we found logistical issues, such as personnel unavailability or lack of IT support as the main barrier, that exceeded the competence of the investigators, causing the data loss. In contrast, the patients' easy understanding of the study protocol and the dedication of the research team during the recruitment and follow-up processes served as facilitators for our study, as both are well-known contributors to the successful achievement of implementation objectives, such as those related to our screening program [28].

4.2. PMI Diagnosis, Incidence, and Characteristics

We defined PMI as hs-cTnT elevation above the 99th upper reference percentile, with a change of more than 50% from preoperative values. These criteria were established based on available information and our clinical experience [25,26,29,30]. Pre and postoperative hs-cTnT concentrations allowed us to differentiate its acute changes from chronic elevations. Our criteria differed from some previous studies that only focused on postoperative hs-cTnT measurements [3,20], used contemporary (i.e., not high sensitivity) cTnT methods [20], or measured high-sensitivity cardiac troponin I (hs-cTnI) [31]. Most of the preoperative samples were obtained in scheduled, non-urgent surgeries during the month before the intervention, while few others were obtained up to 6 months prior. A large intraindividual variability of hs-cTnT over time could be a confounding factor for PMI diagnosis when comparing pre- and postoperative values. Nevertheless, hs-cTnT concentrations have low long-term variability, being 11% in healthy individuals and 8.5% in patients with CVRF or stable coronary disease, like those included in study [32]. Since we used a criterion for PMI diagnosis of a pre to postoperative hs-cTnT variation of $\geq$50%, much higher than the long-term biological variability, we inferred that even samples obtained 6 months before surgery accurately reflected the true troponin value at the time of the intervention.

In our study, PMI was diagnosed in one in six (15.7%) included patients. Despite variations in criteria and observational periods, the elevated PMI incidence in our study concurs with findings from other comparable studies using hs-cTnT as a biomarker, which found a PMI prevalence of 17.9% [1]. Patients with PMI exhibited a higher prevalence of antecedents of CVRF and higher preoperative hs-cTnT concentrations. It was not surprising that PMI patients had significantly higher preoperative hs-cTnT values than patients without PMI, as hs-cTnT is a sensitive biomarker of the cardiac stress associated with pre-existing CVRF and CVD. Furthermore, PMI patients experienced more frequent cardiocirculatory complications during or immediately after surgery. Many of the observed complications, such as hypotension, bleeding, or arrhythmia, can disbalance the equilibrium between cardiac oxygen supply and demand and lead to myocardial injury unrelated to atherothrombosis [33], causing type 2 myocardial infarction. These observations suggested that among our high-risk patients, some were more prone to PMI than others. Elevated hs-cTnT concentrations before surgery, along with the presence of CVRF or CVD, delineated what could be denominated as a "PMI-prone phenotype". Recognizing this phenotype could aid clinicians in providing special attention to these patients during peri- and postoperative periods, as well as during follow-ups outside the hospital. Additionally, PMI was more often observed in patients undergoing urgent surgeries, leading to the hypothesis that the lack of adequate hemodynamic stability or control of pre-existing CV conditions, combined with the stress imposed by the urgent surgical condition, could lead to PMI. Overall, our findings emphasize the importance of systematic PMI screening to identify patients prone to PMI and optimize their health and functional capacity prior to surgery to improve their surgical outcomes [34].

4.3. Outcomes in the Follow-Ups

In the whole cohort, the incidence of MACCE was 4.5%, reaching 9.5% in PMI patients in the first month. A comparable study reported MACCE incidences of 9.0%, although it included patients exclusively undergoing vascular surgery [35]. Another Spanish cohort study observed the incidence of MACCE of 4.3% in intermediate and high-risk surgeries, although the study included fewer patients than ours, with higher stages of cardiac risk or undergoing urgent surgeries and a follow-up period limited to hospitalization [36].

PMI patients had significantly higher rates of MACCE in the first month (9.5% vs. 3.6%) and successive months (8.6% vs. 4.3%) than no-PMI ones. All-cause and cardiovascular death had the same incidence (1.7% and 0.9%, respectively, in both groups) in PMI and no-PMI patients during the first month follow-up. However, at the one-year observation, both all-cause (11.2%) and cardiovascular (3.9%) deaths had sharply increased in PMI patients, outlining the prognostic severity of the condition and emphasizing the importance of systematic screening. Notably, during the months after the first follow-up, PMI showed a high rate of CHF (6.0% of cases). This fact reinforces the importance of systematically detecting PMI during hospitalization, as well as monitoring signs or symptoms of CHF during follow-up. It is suggestive to hypothesize that optimal management of risk factors associated with CHF, such as hypertension, diabetes, obesity, and smoking, can help reduce its occurrence in PMI patients. It was not surprising that some of the PMI patients (1.4%) required coronary revascularization during the one-year follow-up compared with no case in no-PMI patients. This finding aligns with a published meta-analysis [37], which included coronary revascularization trials and defined PMI based on larger biomarker elevations associated with subsequent mortality. In the case of other complications unrelated to the CV system, infection was predominant in the first month (15.9%), but its incidence declined in successive months to 7.7%, which was equal to the incidence of all-cause death (7.0%).

Our cohort included old patients with a high CVRF; they were commonly using cardiovascular drugs. Preoperatively, the use of ACEIs, aspirin, beta-blockers, or oral anticoagulants, ordered by frequency of use, was significantly more prevalent in patients who later experienced PMI. This differential therapeutic pattern remained consistent throughout the entire follow-up period. Statins were widely and similarly used in PMI and no-PMI patients. Thus, the diagnosis of a PMI did not result in a change after surgery in the frequency of drug usage, which could be attributed to the lack of compelling evidence regarding specific treatments for PMI patients. We cannot consider the MANAGE trial [38] launched after our study's beginning, but clinicians implicated in our study relied on the 2014 ESC/EAS (European Atherosclerosis Society) guideline [8], which recommended considering the use of aspirin and statins based on patients' cardiovascular risk factors. Moreover, given that factors observed as PMI-associated pointed to a coronary oxygen disbalance rather than to an atherothrombotic episode as the cause of the myocardial injury, the lack of increased use of aspirin, or anticoagulant/antiplatelet drugs after PMI, as we observed in our study, seemed appropriate.

4.4. Implications for Clinical Practice

The current real experience in implementing hs-cTnT screening can serve as a compelling example for other sites. Our PMI screening yielded significant results in high-risk patients, especially those with a history of CVRF, CVD, or renal impairment. The screening is feasible as it only requires clinical surveillance of patients and routine clinical and laboratory explorations. Identifying PMI patients opens the opportunity to enhance their outcomes. Of note, we identified certain implementation barriers that need to be addressed for the optimal success of the screening program.

4.5. Limitations and Strengths

The main limitation of the study was the incomplete recruitment of all eligible patients. Although we included two-thirds of the eligible patients, the lack of sufficient investigators to conduct assessments during weekends, holidays, or in a timely manner according to

the protocol was a logistical barrier to achieving complete recruitment. The absence of centralized technical assistance through staff departments, such as IT, resulted in a minor limitation in the availability of all registrable data. Tasks like requesting blood samplings, conducting formal cardiology evaluations, and sending follow-up visit reminders were performed manually. However, the investigators were able to overcome this barrier through intense dedication. These implementation barriers could be easily overcome if executive boards or key decision-makers provide support and allocate the necessary resources for the implementation process. We have some limitations in comparing our results with other studies due to the absence of standardized criteria for PMI diagnosis. However, our study design was planned in anticipation and alignment with the most recent guidelines on the topic. Finally, due to the experimental nature of our study, it was solely conducted by the group of researchers involved. Thus, our efforts did not provide enough grounds to incorporate hs-cTnT systematic screening into clinical practice.

The study also has some strengths. The study was developed by an ad hoc established multidisciplinary research team comprising different clinical professionals. This collaborative approach significantly improved the applicability and compliance of our protocol. The study also showed the challenges and complexities that exist in real clinical practice when implementing a local PMI screening program. It highlights that the mere publication and dissemination of guidelines and recommendations do not automatically ensure their rigorous implementation in clinical practice. Factors such as awareness, acceptance, and understanding among healthcare professionals, as well as the availability of necessary resources and infrastructure, are crucial for the successful implementation of new protocols. Finally, an easy understanding of the study protocol and the dedication of the research team during the recruitment and follow-up processes allowed for almost complete compliance of patients in both the one-month and one-year follow-ups.

5. Conclusions

Our study demonstrated the relevance of implementing PMI screening and supported the need for its systematic screening in high-risk patients undergoing elective or urgent noncardiac surgeries. The study also revealed that challenges and complexities exist in real clinical practice when implementing a local PMI screening program. The successful implementation of new protocols in clinical practice will rely not only on the implication of healthcare professionals but also on the availability of necessary resources and infrastructure.

6. Patients

Patients were not involved in the design, conduct, or reporting of this study as it was not applicable to this research project.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm12165371/s1. Table S1: STROBE Statement—Checklist of items that should be included in reports of cohort studies; Table S2: Surgical and anesthetic characteristics of the PMI and no PMI patients; Table S3: Pharmacological treatment for PMI and No-PMI patients before surgery and in the follow-ups. Table S4. Percentages of clinical events observed in the earlier (first month, 1st-m) and subsequent (first month to one year, 1y) follow-up periods.

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Data Availability Statement: The data used in the present study are part of a larger dataset. The datasets generated and analyzed during the current study are available and can be supplied by the corresponding authors upon reasonable request. The data not used for this manuscript will be employed in future manuscripts.

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4.2. ESTUDIO II. Coste-efectividad de la estrategia de cribado sistemático de troponina T cardiaca de alta sensibilidad comparada con la atención habitual para identificar pacientes con lesión miocárdica perioperatoria tras cirugía mayor no cardiaca

Título	**Cost-effectiveness of a high-sensitivity cardiac troponin T systematic screening strategy compared with usual care to identify patients with peri-operative myocardial injury after major noncardiac surgery**
Referencia	Popova E, Alonso-Coello P, Álvarez-García J, Paniagua-Iglesias P, Rué-Monné M, Vives-Borrás M, Font-Gual A, Gich-Saladich I, Martínez-Bru C, Ordóñez-Llanos J, Carles-Lavila M. Eur J Anaesthesiol. 2023 Mar 1;40(3):179-189. doi: 10.1097/EJA.0000000000001793. Epub 2023 Jan 11. Erratum in: Eur J Anaesthesiol. 2023 Sep 1;40(9):717. PMID: 36722187.
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4.2.1. Resumen de resultados del segundo estudio

Los pacientes incluidos en el análisis de coste-efectividad fueron los 1477 pacientes del estudio anteriormente descrito (estudio I).

- *Coste-efectividad*

La estrategia de cribado sistemático con TncT-as permitió detectar 208 casos adicionales de LMP en comparación con la atención habitual. El cribado identificó 232 casos de LMP con una incidencia del 15,7%; la estrategia de atención habitual identificó únicamente 24 casos de LMP con una incidencia del 1,6%. El coste incremental total para los 1477 pacientes entre las dos estrategias fue de 88 394€; en consecuencia, el ICER fue de 425€ euros para cada uno de los 208 casos de LMP detectados adicionalmente.

- *Análisis de sensibilidad determinista*

En el primer análisis de sensibilidad determinista, el diagrama de tornado (Tornado 1) mostró que un empeoramiento de los valores predictivos implicaba un aumento en el valor de ICER. El valor predictivo negativo tuvo el mayor impacto sobre el valor final de ICER (su disminución del 1% aumentó un 2,2% del ICER).

En el segundo análisis de Tornado (Tornado 2), en términos de costes, demostró que un aumento de los costes implicaba un aumento del ICER. El parámetro con mayor impacto sobre el ICER fue la medición de TncT-as (su aumento de 15% en el coste incrementó el ICER en un 9% aproximadamente).

- *Análisis de sensibilidad probabilística*

En el análisis de sensibilidad probabilístico, de acuerdo con la curva CEAC, al aumentar la disposición a pagar (WTP), se incrementó la probabilidad de que la estrategia de cribado sistemático con TncT-as fuera considerada más coste-efectiva. Así, cuando la WTP era de 425 € (valor de la ICER), el 50% de las simulaciones de Monte Carlo fueron coste-efectivas y cuando la WTP llegó a 780 €, el porcentaje de iteraciones coste-efectivas alcanzó el 100%.

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ORIGINAL ARTICLE

Cost-effectiveness of a high-sensitivity cardiac troponin T systematic screening strategy compared with usual care to identify patients with peri-operative myocardial injury after major noncardiac surgery

Ekaterine Popova, Pablo Alonso-Coello, Jesús Álvarez-García, Pilar Paniagua-Iglesias, Montserrat Rué-Monné, Miguel Vives-Borrás, Adria Font-Gual, Ignasi Gich-Saladich, Cecilia Martínez-Bru, Jordi Ordóñez-Llanos* and Misericordia Carles-Lavila*

BACKGROUND About 300 million surgeries are performed worldwide annually and this figure is increasing constantly. Peri-operative myocardial injury (PMI), detected by cardiac troponin (cTn) elevation, is a common cardiac complication of noncardiac surgery, strongly associated with short- and long-term mortality. Without systematic peri-operative cTn screening, most cases of PMI may go undetected. However, little is known about cost effectiveness of a systematic PMI screening strategy with high-sensitivity cardiac troponin T (hs-cTnT) after noncardiac surgery.

OBJECTIVE To assess, in patients with high cardiovascular risk, the cost-effectiveness of a systematic screening strategy using a hs-cTnT assay, to identify patients with PMI after major noncardiac surgery, compared with usual care.

DESIGN Cost-effectiveness analysis; single centre prospective cohort study.

SETTING Spanish University Hospital.

PATIENTS From July 2016 to March 2019, we included 1477 consecutive surgical patients aged ≥65 or if <65, with documented history of cardiovascular disease or impaired renal function, who underwent major noncardiac surgery and required at least an overnight hospital stay. We excluded patients aged <65 years without cardiovascular disease, undergoing minor surgery, or with an expected <24 h hospital stays.

INTERVENTIONS We conducted a decision-tree analysis, comparing a systematic screening strategy measuring hs-cTnT before surgery, and at the 2nd and 3rd days after surgery vs. a usual care strategy. We considered a third-party payer perspective and the outcomes of both strategies in the short-term (30 days follow-up). Information about costs was expressed in Euros-2021. We calculated the incremental cost-effectiveness ratio (ICER) of the systematic hs-cTnT strategy, defined as the expected cost per any additional PMI detected, and explored the robustness of the model using deterministic and probabilistic sensitivity analysis.

MAIN OUTCOME MEASURES ICER of the systematic hs-cTnT screening strategy.

RESULTS The ICER was €425 per any additionally detected PMI. The deterministic sensitivity analysis showed that a 15% variation in costs, and a 1% variation in the predictive values, had a minor impact over the ICER, except in case of the negative predictive value of the systematic hs-cTnT screening strategy. Monte Carlo simulations (probabilistic sensitivity analysis) showed that systematic hs-cTnT

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screening would be cost-effective in 100% of cases with a 'willingness to pay' of €780.

CONCLUSIONS Our results suggest that systematic peri-operative PMI screening with hs-cTnT may be cost-effective in the short-term in patients undergoing major noncardiac surgery. Economic evaluations, with a long-term horizon, are still needed.

TRIAL REGISTRATION Clinicaltrials.gov identifier: NCT03438448.

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KEY POINTS

- Detects more peri-operative myocardial injury cases than the usual care strategy.
- May be cost-effective in the short-term at reasonable expenditure.
- May be implemented in this group of patients, as recommended in the most recent guidelines.

Introduction

Approximately, 300 million surgeries are performed worldwide annually, and numbers are increasing constantly. Recent evidence suggests that postoperative death is the third cause of mortality, accounting for 7.7% of deaths.[1] Peri-operative cardiovascular events are the leading cause of morbidity and mortality in noncardiac surgery patients.[2–4]

The recent ESC/ESAIC guideline[5] defines peri-operative myocardial injury (PMI) as an acute cardiomyocyte injury detected by the postoperative release of cardiac troponin (measured with a high-sensitivity assay), with or without accompanying symptoms, and with or without ECG or imaging evidence of acute myocardial ischaemia. PMI could have cardiac or noncardiac origins and is the most frequent cardiac complication in noncardiac surgery patients, being strongly associated with 30-day mortality.[5,6] Cardiac troponin is the only biomarker recommended to diagnose PMI, due to its cardiac specificity.[2–6] Over the last years, most hospitals have replaced contemporary cardiac troponin (cTn) assay with the new generation high-sensitivity cTnT (hs-cTnT) assays, which provides optimal diagnostic performance and better precision for early detection of myocardial injury.[7] Without systematic peri-operative cTn screening, most cases of PMI are undetected.[6] Nowadays, peri-operative guidelines are increasingly recommending the screening of high-risk surgical patients, by measuring hs-cTnT.[5,8–10] Screening programs have become usual practice in some hospitals of North America and Europe,[6,11] nevertheless, they are still not commonly implemented in Spain.

Despite this emerging healthcare policy, little is known about the economic evaluation of cTn screening after major noncardiac surgery in high-risk patients. However, the few available studies, despite using different approaches and being carried out in different contexts, show comparable results, screening being probably cost-effective in the short term.[12–14] The aim of this study was to perform a cost-effectiveness analysis, using a hs-cTnT systematic screening program for PMI detection in high-risk patients, after major noncardiac surgery at a Spanish University Spanish hospital, and compare it with a usual detection strategy.

Methods

Design

Cost-effectiveness analysis; single centre prospective cohort study. The study was registered at Clinicaltrials.gov (NCT03438448). We adhered to the CHEERS 2022 reporting guidelines for economic evaluations (Consolidated Health Economic Evaluation Reporting Standards 2022) (Table S1, Supplemental Digital Content, http://links.lww.com/EJA/A796).

Ethics

Ethics approval for this study was provided by Dr Alonso-Martinez M, MD as Technical Secretary of the Ethics Committee of Clinical Investigation at Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, on 11 May 2016, with unique Protocol ID: IIBSP-IMP-2015-95. Written informed consent was obtained from all included patients before inclusion.

Study population

From July 2016 to March 2019, in the systematic hs-cTnT strategy, we consecutively included 1477 high-risk cardiovascular patients aged ≥65 or younger with a documented history of cardiovascular disease (coronary artery disease, chronic heart failure, stroke, or peripheral vascular disease) or with impaired renal function (estimated glomerular filtration rate $<60\,ml\,min^{-1}\,1.73\,m^{-2}$), who underwent elective or urgent major noncardiac surgery (orthopaedic, traumatological, spinal, visceral, digestive, peripheral vascular, thoracic, gynaecological, plastic, or otorhinolaryngological), and had hospital admission including at least one overnight stay. Patients were identified during preoperative assessment. We excluded patients aged <65 years without cardiovascular diseases, undergoing minor surgery, or with an expected <24 h hospital stay. A detailed version of the study protocol was

published in a peer-reviewed journal.[15] In the usual care strategy, the same 1477 patients included in the systematic hs-cTnT screening strategy were analysed as a hypothetical cohort, assuming that hs-cTnT measurement was only triggered by the existence of signs or symptoms of cardiac ischaemia.

High-sensitivity cardiac troponin measurements and peri-operative myocardial injury definition

hs-cTnT was measured by an electrochemiluminescent immune assay (Roche Diagnostics, Basel, Switzerland) with a measuring range of 5.0–10 000 ng l^{-1}, a limit of detection 5.0 ng l^{-1}, a 99th upper reference percentile (URL) of 14 ng l^{-1},[16] and a 10% coefficient of variation of 13 ng l^{-1}. The systematic hs-cTnT strategy considered the measurement of hs-cTnT at three predefined time points: preoperatively (in the preoperative visit or just before surgery), and at 2nd and 3rd days after surgery. In this strategy, we defined PMI as a hs-cTnT higher than the URL of ≥14 ng l^{-1}, with a ≥50% increase above the preoperative value[17] by the second or third day after surgery, resulting from cardiac causes, with or without cardiac ischaemic symptoms or electrocardiographic (ECG) changes. In patients with confirmed PMI a ''formal'' cardiology evaluation was carried out. All the cardiologists involved approved the study protocol. We excluded patients whose hs-cTnT elevation was considered to result from a nonischaemic aetiology (e.g., sepsis, pulmonary embolism, cardioversion, and others). In the usual care strategy, we defined PMI as the presence of postoperative ischaemic signs and symptoms, with or without ECG changes, together with an elevated hs-cTnT of ≥14 ng l^{-1} at days 2 and 3 after surgery.

Model design

We used a decision-tree model to estimate the cost-effectiveness of systematic hs-cTnT screening, compared with usual care (hs-cTnT screening only triggered by the existence of signs or symptoms), considering a 30-day follow-up, and a third-party payer perspective (Fig. 1). Since our usual care strategy was assessed in a hypothetical cohort including the same patients as at the systematic hs-cTnT screening strategy, effectiveness data was estimated from the study cohort, using as endpoint any detected PMI. Given that we conducted a short-term (30 days follow-up) decision-tree analysis, it was not necessary to apply a discount rate. Incidence of PMI and the number of performed procedures were obtained from the study cohort for both compared strategies. Information about costs was obtained from the hospitals' accounting department. All costs were calculated and expressed in Euros (€), 2021 value. We calculated the incremental cost-effectiveness ratio (ICER), defined as the expected cost per additionally detected PMI. We explored model robustness using deterministic and probabilistic sensitivity analysis. We ran the model within TreeAge Pro Software version 2021 R1.1.[18]

High-sensitivity cardiac troponin T screening strategy

In the hs-cTnT screening strategy, for PMI patients fulfilling myocardial infarction (MI) criteria, additional interventions, like coronary angiography or percutaneous coronary intervention, were performed to confirm the MI diagnosis and treat the vessel lesions. Aspirin and/or statins were administered as needed, according to clinical judgement. Patients were followed-up by telephone at 30 days after the date of surgery. The systematic screening strategy considered four possible health states: true-positives (PMI confirmed by hs-cTnT elevation), true-negatives (no PMI defined by no hs-cTnT elevation), false-positives (hs-cTnT elevation due to nonischaemic causes), and false-negatives (confirmed PMI without hs-cTnT elevation during the postoperative period).

Usual care strategy

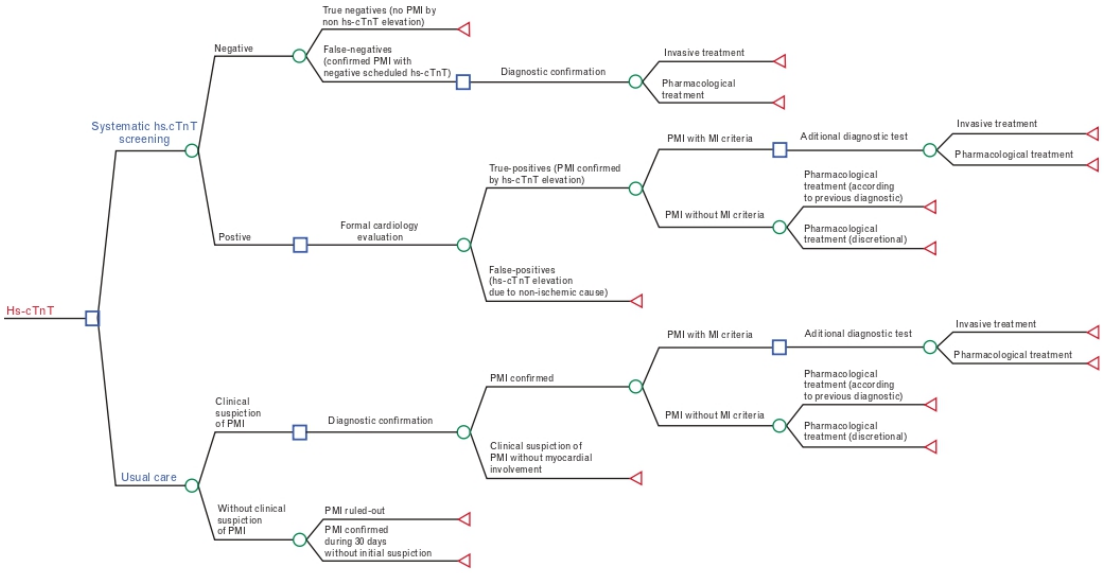
The usual care strategy, conducted similarly to a previous study in Canada,[14] was a hypothetical cohort, which solved the lack of information about the evolution of undetected PMI cases. Information was obtained studying the same patients within the systematic hs-cTnT screening strategy cohort. In the usual care strategy, health professionals managed patients with or without clinically suspected PMI, according to their clinical practice. In patients with signs or symptoms of cardiac ischaemia, when PMI was confirmed by the diagnostic tests including hs-cTnT measurements, patients were considered as true-positives, or when PMI was ruled out, as false-positives. In patients without signs or symptoms, those developing PMI during the 30 days after surgery were considered as false-negatives, whereas those free of complications were considered as true-negatives. Based on local experts' considerations, as well as on the available literature,[14] the incidence of PMI suspected by symptoms as chest pain, but without myocardial involvement was assumed to be 1%.

Resource utilization and cost estimation

The study was carried out from a third-party payer perspective, considering only direct health costs, including tests and treatments applied in both strategies, as well as the financial cost of the time expended by healthcare professionals.

For the systematic screening strategy, we distinguished between costs of screening tests, diagnostic confirmation, treatment and 30-day follow-up costs. Resource use for all health states included hs-cTnT measurements and 30-day follow-up. However, three states, with the exception of true-negatives incurred more additional resources: true-positives: diagnostic confirmation (ECG and echocardiography), formal cardiologist evaluation, additional tests with/without invasive treatment (coronary angiography or percutaneous coronary intervention), and/or pharmacological treatment (aspirin and/or statin); false-positives: formal cardiologist evaluation; and false-

Fig. 1 Decision tree model used to evaluate the cost-effectiveness of systematic hs-cTnT screening vs. usual care.



hs-cTnT, high-sensitivity cardiac troponin T; MI, myocardial infarction; PMI, peri-operative myocardial injury.

negatives: when PMI was confirmed at 30 days, diagnostic confirmation with more invasive and/or pharmacological treatment.

In the usual care strategy, there were neither systematic hs-cTnT measurements, nor 30-day follow-up costs. In the case of suspected PMI (true-positives at the systematic hs-cTnT screening strategy), the following were considered as 'resources': diagnostic confirmation (ECG, echocardiography and hs-cTnT measurements), formal cardiologist evaluations, additional tests with/without invasive treatment (coronary angiography or percutaneous coronary intervention), and/or pharmacological treatment (aspirin and/or statin). When PMI was ruled out by absence of ischaemic signs or symptoms (false-positives at the screening strategy), we considered only initial diagnostic confirmation. There were no cost considerations for the true-negatives, and false-negatives, as these patients usually are not followed-up in a usual care strategy.

We considered all costs corresponding to pharmacological treatment (aspirin and/or statin), prescribed during the 30-day study period, regardless of whether those patients were or were not taking aspirin and/or statins previously. At the time of study design, pharmacological management of PMI patients was not established, and use of statins and aspirin in noncardiac surgery patients was based on their individual cardiovascular risk factors.[8] Although the use of statins was well accepted, aspirin remained controversial in PMI due to the increased risk of bleeding. As our protocol was based on the ESC/EAS guidelines, the decision to discontinue, continue or newly prescribe statins and/or aspirin was at clinical discretion based on patients' individual cardiovascular status. Finally, no major changes in pharmacological treatment were applied after surgery in our population; consequently, neither a significant increase nor decrease of treatment related costs were observed. Average costs included in our decision-tree model (Fig. 1), together with the effectiveness for each health state included in both strategies, as well as observed effects and probabilities are shown in Table 1. The model performance measures and costs are shown in Table 2.

Analysis

We compared the relative costs and effects of both strategies, calculating the ICER, which indicates the additional cost for an additional detected PMI case. The model robustness was explored using deterministic and probabilistic sensitivity analysis. First, we performed a Tornado deterministic sensitivity analysis, to test multiway effects on the results of our model. The Tornado diagram assumes a plausible range of the initial values of included variables, and analyses their impact over the ICER, ranking the results from major to minor impact.

We conducted two Tornado analyses. In the first one we included the positive and negative predictive values for

both strategies, considering as a plausible range of ±1% of the baseline value. In the second one, we included all cost variables: hs-cTnT measurements, formal cardiologist evaluation, 30-day follow-up, pharmacological treatments (aspirin and statins for 30 days), diagnostic confirmation (ECG, echocardiography), invasive treatment (percutaneous coronary intervention), and additional diagnostic test (coronary angiography), with ±15% variation, which permits the highest probability of a price variation to be reflected.

In addition, we conducted a probabilistic sensitivity analysis, using second-order Monte Carlo simulations, in which all parameters simultaneously randomly varied across 10 000 iterations, creating joint distributions of costs and effects, which simultaneously represent the uncertainty presented in each variable. The type of distribution used for the different variables was the *beta* distribution used for parameters of probabilities, whereas the *gamma* distribution was used for the cost data.[19] The results of probabilistic sensitivity analysis are shown in the cost-effectiveness acceptability curve (CEAC). This allowed the percentage of iterations (Y-axis) in which the strategies could be cost-effective to be observed, depending on the 'willingness to pay' (WTP) threshold (X-axis).

Willingness to pay

The WTP is the maximum cost that a society would be willing to pay for any additional PMI detected. To our knowledge, there is no available literature providing a specific WTP value for screening PMI in high-risk, major noncardiac surgery patients. Therefore, we examined the evolution of the CEAC curve for different WTP values, taking the ICER's value as the central point of the threshold of willingness to pay.

Results

We included 1477 patients; most of them (1399; 94.8%) were aged ≥65 years and more than half (843; 57.2%) were women. Baseline characteristics of the patients according to their health status are presented in Table 3. The accuracy to detect or rule-out PMI was 98.9% (1461); the remaining cases were 0.8% (12) false-positives and 0.3% (4) false-negatives. The true-positives for PMI (232; 15.7%), compared with the true-negatives (1229; 83.2%), were more likely to have a history of congestive heart failure (15.1 vs. 6.4%), atrial fibrillation (24.1 vs. 13.5%), renal failure (31.2 vs. 15.7%), anaemia (19.4 vs. 10.2%), as well as emergency surgery (41.1 vs. 26.0%), despite not reaching a significant statistical difference.

Cost-effectiveness

Our cost-effectiveness model showed that an increase of effectiveness was correlated with an increase in costs. The systematic hs-cTnT screening strategy detected 10-times more PMI cases ($n = 232$, 15.7%) than the usual care strategy ($n = 24$, 1.6%). The total incremental cost of the systematic hs-cTnT screening strategy was €88 394 for the 1477 patients (€59.8 per patient); accordingly, the ICER was €425 for each of the 208 PMI cases additionally detected (Table 4).

Deterministic and probabilistic sensitivity analysis

As expected, in our Tornado deterministic sensitivity analysis, an improvement in predictive values implied a reduction on the ICER's value. The impact over the

Table 1 Model inputs: average costs, observed effects, probabilities and included parameters.

Parameters Health states Systematic hs-cTnT screening strategy	Point estimate *n* (%)	Source
True positives		
PMI with MI* criteria and invasive treatment**	1 (0.068)	Study cohort
PMI with MI criteria and pharmacological treatment ***	6 (0.406)	Study cohort
PMI without MI criteria and pharmacological treatment according to previous diagnosis	2 (0.135)	Study cohort
PMI without MI criteria and discretionary pharmacological treatment	223 (15.098)	Study cohort
True negatives	1229 (83.21)	Study cohort
False positives	12 (0.812)	Study cohort
False negatives	4 (0.271)	Study cohort
Usual care strategy		
Clinical suspicion of PMI (as true positives)		
PMI with MI criteria and invasive treatment	2 (0.14)	Study cohort
PMI with MI criteria and pharmacological treatment	5 (0.34)	Study cohort
PMI without MI criteria and discretionary pharmacological Treatment	17 (1.14)	Study cohort
PMI ruled-out (as true negatives)	1230 (83.3)	Study cohort
Clinical suspicion of PMI, without myocardial involvement (as false positives)	15 (1)	Clinical experts
PMI confirmed for 30 days, without initial suspicion (as false negatives)	208 (14.08)	Study cohort
Observed effects	***n***	
PMI detected by systematic hs-cTnT screening	232	Study cohort
PMI detected by usual care	24	Study cohort

hs-cTnT, high-sensitivity cardiac troponin T; MI, myocardial infarction; PMI, peri-operative myocardial injury. * Myocardial infarction. ** Percutaneous coronary intervention. *** Aspirin and statin for 30 days.

Table 2 Model performance measures, costs, and their plausible range.

Performance measures	Baseline value	Plausible range on tornado diagram	Source
Systematic hs-cTnT screening			
Positive predictive value	0.951	0.941–0.960	Diagnostic algorithms
Negative predictive value	0.997	0.981–1.000	Diagnostic algorithms
Usual care			
Positive predictive value	0.615	0.609–0.622	Diagnostic algorithms
Negative predictive value	0.855	0.847–0.864	Diagnostic algorithms
Costs (€–2021)			
Used parameters			
hs-cTnT measurements	35.1	29.8–40.4	Hospitals' Accounting department
Formal cardiologist evaluation	131	111–150	Hospitals' Accounting department
30 days follow-up	5.20	4.42–5.98	Hospitals' Accounting department
Pharmacological treatment* (discretional)	20.4	17.3–23.4	Catalan Institute of health
Diagnostic confirmation (ECG and echocardiography)	117	99.8–135.	Hospitals' Accounting department
Invasive treatment**	3393	2884–3902	Catalan Institute of health
Pharmacological treatment* (according to previous diagnostic)	40.7	34.6–46.8	Catalan Institute of health
Additional diagnostic test (coronary angiography)	1558.6	1324–1792	Catalan Institute of health

hs-cTnT, high-sensitivity cardiac troponin T. * Pharmacological treatment: aspirin and statin for 30 days. ** Invasive treatment: percutaneous coronary intervention.

ICER was lower than initial variation (±1%) in all included variables, except for the negative predictive value of the systematic screening strategy, where a 1% decrease in variation increased the ICER's value by up to 2.2% (first blue line to the right side of expected value in Fig. 2a), from €425 to €434. This highlights the importance of the negative predictive value over the ICER's final value. Figure 2a, shows the impact of the variation of positive and negative predictive values of both strategies over baseline values.

In terms of costs, in our second Tornado diagram (Fig. 2b), hs-cTnT measurements (ICER's value from €387 to €462), followed by the formal cardiologist evaluation (ICER's value from €402 to €448) were the variables with greater effect over the ICER. Figure 2b shows the impact of the variation of positive and negative predictive values of both strategies over baseline values (red/blue lines to the right side of the expected value [EV]). The impact over the ICER was never >9%, which was less than the initial introduced variation (±15%).

In the probabilistic sensitivity analysis, the CEAC shows the percentage of cost-effective Monte Carlo iterations (*y*-axis), as the WTP threshold increases (*x*-axis, Fig. 3). According to our CEAC, when WTP increases the probability that systematic hs-cTnT screening strategy is considering cost-effective, increases. When the threshold value is the ICER's value (€425), the systematic hs-cTnT screening strategy obtained 50%

Table 3 Baseline characteristics by condition in the systematic hs-cTnT screening strategy.

Characteristics	All (*n* = 1477)	True-positive (*n* = 232)	True-negative (*n* = 1229)	False-positive (*n* = 12)	False-negative (*n* = 4)
Age ≥65 years	1399 (94.8)	223 (96.1)	1172 (94.5)	11 (91.7)	4 (100.0)
Sex female	843 (57.2)	135 (58.2)	706 (57.1)	8 (66.7)	2 (50.0)
Background conditions					
Hypertension	1048 (71.0)	187 (80.6)	857 (69.1)	8 (66.7)	4 (100.0)
Diabetes mellitus	364 (24.7)	72 (31.0)	289 (23.3)	3 (25.0)	3 (75.0)
Hypercholesterolaemia	751 (50.9)	128 (55.2)	621 (50.1)	8 (66.7)	2 (50.0)
Coronary artery disease	185 (12.5)	41 (17.7)	144 (11.6)	4 (33.3)	0 (0.0)
Congestive heart failure	114 (7.7)	35 (15.1)	79 (6.4)	2 (16.7)	0 (0.0)
Atrial fibrillation	223 (15.1)	56 (24.1)	157 (13.5)	5 (41.7)	0 (0.0)
Stroke	104 (7.1)	24 (10.3)	80 (6.5)	1 (8.3)	0 (0.0)
Transient ischemic accident	42 (2.8)	11 (4.7)	31 (2.5)	1 (8.3)	0 (0.0)
Peripheral artery disease	153 (10.4)	32 (13.8)	121 (9.8)	3 (25.0)	0 (0.0)
Pulmonary embolism	21 (1.4)	1 (0.4)	20 (1.6)	0 (0.0)	0 (0.0)
Deep vein thrombosis	30 (2.09	5 (2.2)	25 (2.0)	1 (8.3)	0 (0.0)
Chronic obstructive pulmonary disease	200 (13.6)	27 (11.6)	170 (13.7)	1 (8.3)	3 (75.0)
Renal failure	267 (18.1)	72 (31.2)	194 (15.7)	3 (25.0)	1 (25.0)
Anaemia	172 (11.7)	45 (19.4)	126 (10.2)	3 (25.0)	1 (25.0)
Prior treatment with aspirin	395 (26.8)	81 (34.9)	313 (25.3)	5 (41.7)	1 (25.0)
Prior treatment with statins	656 (44.5)	111 (47.8)	543 (43.9)	9 (75.0)	2 (50.0)
Priority of surgery (emergency)	418 (28.4)	95 (41.1)	322 (26.0)	5 (41.7)	1 (25.0)

hs-cTnT, high-sensitivity cardiac troponin T.

Table 4 Peri-operative myocardial injury detection results.

Strategies	Total direct costs (per patient)	Incremental cost* (per patient)	PMI detected	Incremental PMI cases detected	ICER
Usual care	22 826 (15.4)		24		
Systematic hs-cTnT screening strategy	111 221 (75.3)	88 394 (59.8)	232	208	425

hs-cTnT, cardiac troponin T measured with a high-sensitivity method; ICER, incremental cost-effectiveness ratio; PMI, perioperative myocardial injury. *All costs are expressed as 2021 Euros.

of cost-effectiveness simulations, but when WTP equals to €780 the percentage of cost-effective iterations reaches 100%.

Discussion

Main findings

In our study, the systematic hs-cTnT screening of patients at high cardiovascular risk and undergoing major noncardiac surgery, detected 10 times more PMI than the usual care strategy (15.7% vs. 1.6%). Both, the high rate of PMI and the superiority of the systematic hs-cTnT screening strategy can be attributed to the use of a cardiac ischemia biomarker more sensitive and specific than symptoms; chest pain is missed by the frequent use of sedation and analgesia in a postoperative setting.[2–6] The low sensitivity of the usual care strategy to detect PMI raises concerns about its appropriateness. The high proportion of detected PMI in our study may be also explained by the characteristics of our population, with a very large proportion of elderly patients (94.8% ≥65 years) and the inclusion of only patients with high cardiovascular risk.[20,21] Patients with high cardiovascular risk (elderly age, hypertension, type 2 diabetes, atherosclerosis or impaired renal function) usually have hs-cTnT concentrations higher than the upper reference limit of the general population and, therefore, could potentially be diagnosed as false positives. However, systematic preoperative hs-cTnT measurement, as in our study, is currently recommended,[22,23] allowing to differentiate acute PMI from chronically elevated hs-cTnT values in postoperative settings.

Our results suggest that systematic peri-operative hs-cTnT screening in high-risk patients undergoing noncardiac surgery is not only of clinical value but may be cost-effective, in the short-term. The cost per any additional PMI detected by the systematic hs-cTnT screening strategy was €425, with a total incremental cost of €59.8 per patient, compared with the usual care strategy. However, as mentioned, the systematic hs-cTnT screening strategy was ten times more effective than the usual care strategy for PMI detection. Based on the results of the deterministic sensitivity analysis, we may state that our model was robust regarding the variations in costs and predicted values, for both strategies. The most relevant feature in the deterministic sensitivity analysis was that a 1% decrease in the negative predictive value of the systematic hs-cTnT screening strategy increased the ICER's value by 2.2%. In contrast, the probabilistic sensitivity analysis showed that the systematic hs-cTnT screening strategy was the best choice for PMI detection, with a 50% chance of being cost-effective in Monte Carlo simulations when the WTP was €425 (ICER's value), and reaching a 100% when the WTP was €780.

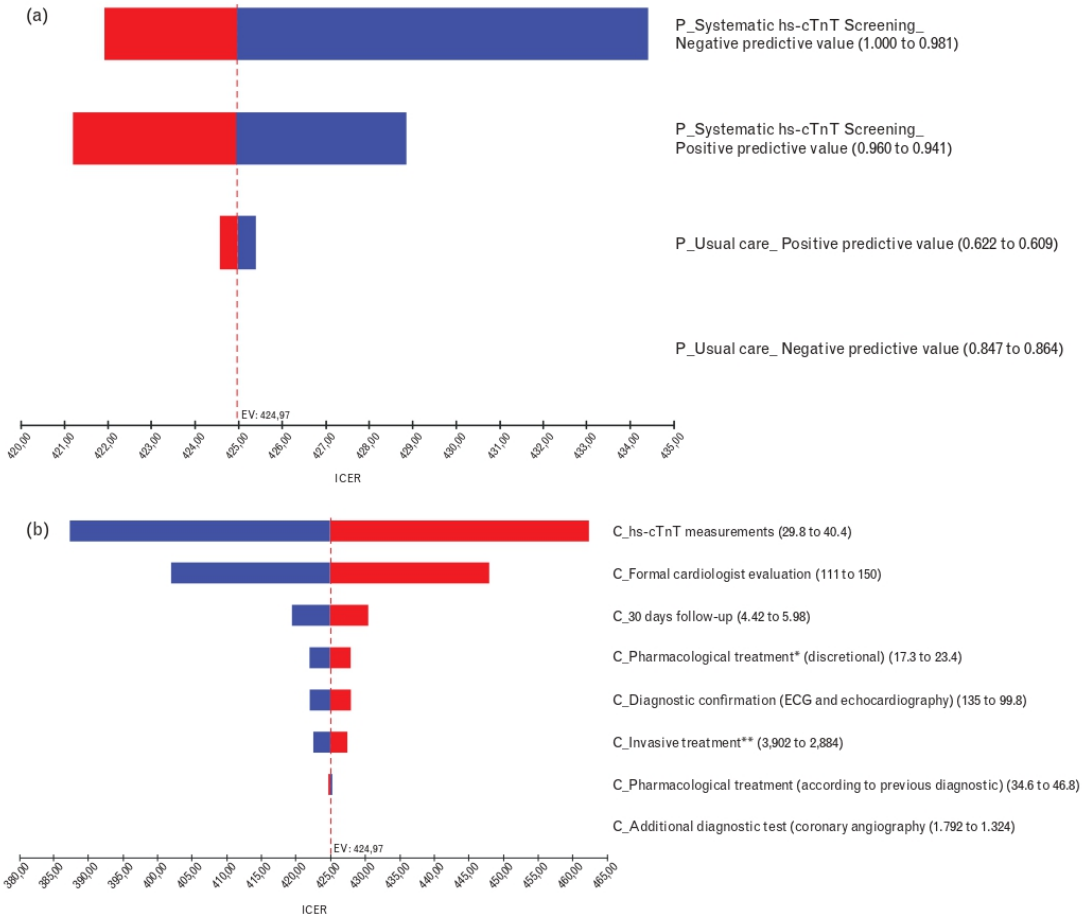
Our results in the context of previous research

The incidence of PMI (15.7%) in our study is comparable with that of other hs-cTn screening programmes.[22] In our cohort, pharmacological treatment with aspirin and/or statins in postoperative period was considered on an individual patient basis, according to each patient's cardiovascular risk factors. Since our study included many elderly patients with an increased frequency of cardiovascular risk factors before surgery, the use of aspirin (34.9%) and statins (47.8%) in our population was frequent and maintained without major changes after the surgery. Consequently, no significant increase of treatment-related costs was observed due to the drug use. Among the drugs proposed for managing patients with PMI, statins were largely used, where trials[24,25] and metanalysis[26] showed that their pre and peri-operative administration reduces not only PMI occurrence but also that of myocardial infarction, stroke, and both cardiac and all-cause mortality. This was not surprising, given than many PMIs could be attributable to coronary atherosclerosis. However, the use of antithrombotic therapies in noncardiac surgery patients is controversial; some studies showing a reduction of major cardiovascular complications with their use,[24] whereas some others found an increased risk of bleeding.[27] This evidence was included in the 2014 ESC/EAS guideline[8] that recommended considering the use of statins, and particularly of aspirin in noncardiac surgery patients based on patients' cardiovascular risk factors. Our protocol design followed such a guideline recommendation. Dabigatran[28] was not included because data on the efficacy of its use was only published in 2018, when our study was already in progress.

At present, there is no evidence from randomised controlled trials or meta-analyses about the effectiveness of systematic hs-cTnT screening in high-risk noncardiac surgery patients. There are only a few economic studies including a broad spectrum of noncardiac surgeries that suggest, despite differences in methodology, that systematic contemporary cardiac troponin screening in noncardiac surgery patients maybe cost-effective.

Mantha *et al.*[12] conducted a study using the Markov-based decision analysis model to determine the cost-effectiveness

Fig. 2 (a) Tornado diagram; impact of the ±1% variation over performance measures. (b) Tornado diagram; the impact of the ±15% variation over baseline value of the costs.

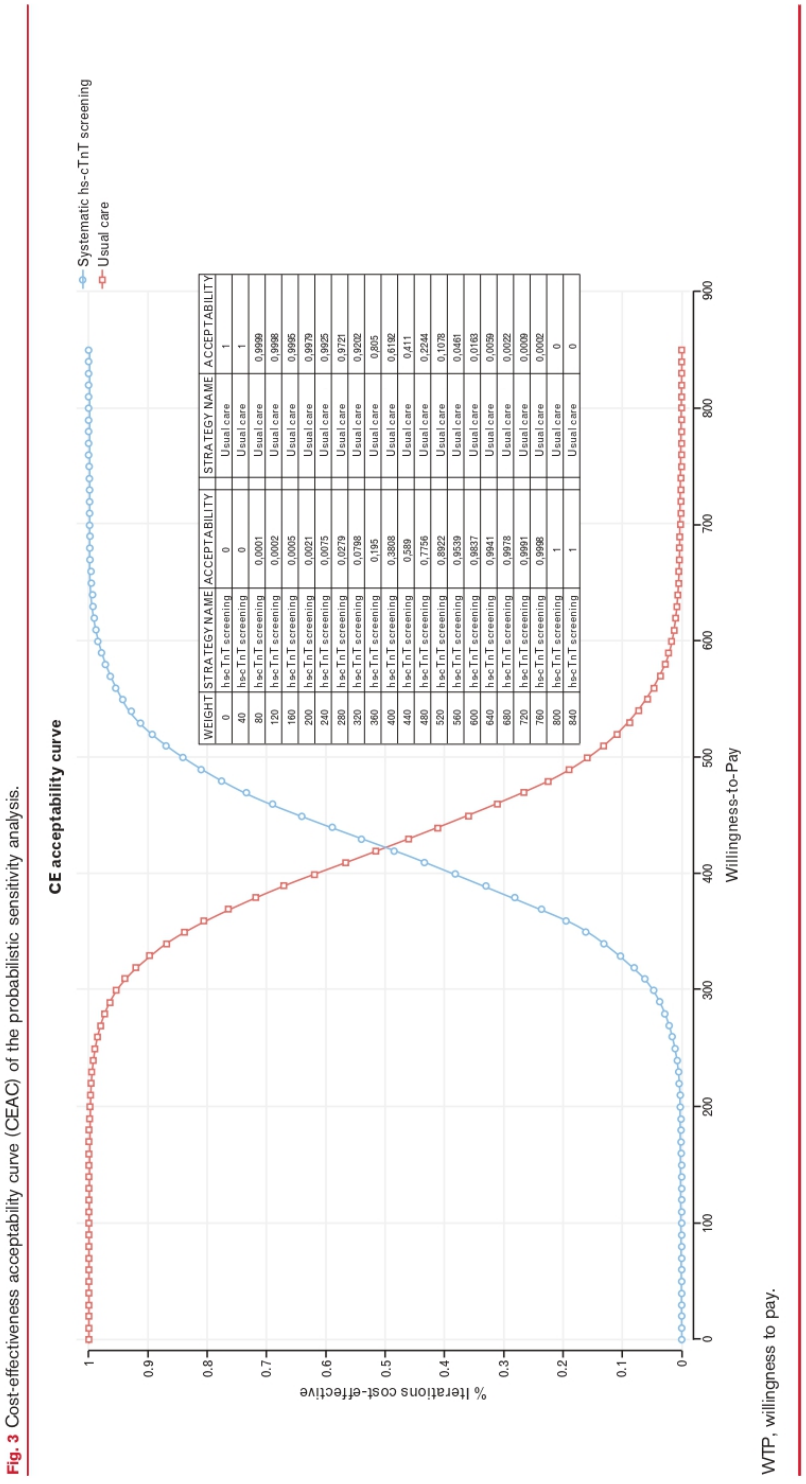


EV, expected value, ICER, incremental cost-effectiveness ratio, *P*, probability. C, costs, EV, expected value, ICER, incremental cost-effectiveness ratio. *Pharmacological treatment: aspirin and statin for 30 days. **Invasive treatment: percutaneous coronary intervention.

of routinely preoperative screening with a contemporary troponin I (cTn I) assay. The study included patients aged ≥65 years undergoing open abdominal aortic aneurysm repair. The model inputs were obtained from the published literature, and the model was designed to assess health outcomes, i.e., quality-adjusted life years (QALYs) and costs (present value of future expenditures). The authors concluded that in patients submitted to elective open abdominal aortic aneurism surgery, a cTn I screening program was cost-effective ($12 641 per QALY).

Torborg *et al.*[13] conducted a pharmaco-economic analysis, to determine the cost-effectiveness of postoperative screening using contemporary cardiac troponin T (cTn T) in patients aged ≥45 years after noncardiac surgery. In their model, the authors assumed a 25% relative risk reduction in 30-day rates of cardiovascular mortality and myocardial infarction after initiation of treatment with aspirin and statins in patients with elevated cTn levels. The authors concluded that routine cTn screening was potentially cost-effective when therapy with aspirin and statins was initiated in patients with elevated cTn.

Finally, Lurati Buse *et al.*[14] developed a model-based cost-consequence analysis and used the data from Canadian patients enrolled in the VISION study (≥45 years undergoing noncardiac surgery, screening with cTn T). The authors concluded that despite moderate costs



WEIGHT	STRATEGY NAME	ACCEPTABILITY
0	hs-cTnT screening	0
40	hs-cTnT screening	0
80	hs-cTnT screening	0,0001
120	hs-cTnT screening	0,0002
160	hs-cTnT screening	0,0005
200	hs-cTnT screening	0,0021
240	hs-cTnT screening	0,0075
280	hs-cTnT screening	0,0279
320	hs-cTnT screening	0,0798
360	hs-cTnT screening	0,195
400	hs-cTnT screening	0,3808
440	hs-cTnT screening	0,589
480	hs-cTnT screening	0,7756
520	hs-cTnT screening	0,8922
560	hs-cTnT screening	0,9539
600	hs-cTnT screening	0,9837
640	hs-cTnT screening	0,9941
680	hs-cTnT screening	0,9978
720	hs-cTnT screening	0,9991
760	hs-cTnT screening	0,9998
800	hs-cTnT screening	1
840	hs-cTnT screening	1
0	Usual care	1
40	Usual care	1
80	Usual care	0,9999
120	Usual care	0,9998
160	Usual care	0,9995
200	Usual care	0,9979
240	Usual care	0,9925
280	Usual care	0,9721
320	Usual care	0,9202
360	Usual care	0,805
400	Usual care	0,6192
440	Usual care	0,411
480	Usual care	0,2244
520	Usual care	0,1078
560	Usual care	0,0461
600	Usual care	0,0163
640	Usual care	0,0059
680	Usual care	0,0022
720	Usual care	0,0009
760	Usual care	0,0002
800	Usual care	0
840	Usual care	0

Fig. 3 Cost-effectiveness acceptability curve (CEAC) of the probabilistic sensitivity analysis.

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associated with cTn T screening in this population, implementation of a monitoring program using cTn T may be potentially relevant, particularly in patients at high risk for myocardial injury after noncardiac surgery (MINS). However, as cTn T was measured using a method with lower analytical and clinical sensitivity that the current existing hs-cTnT assays, that strategy could miss some MINS cases.

Results of our study support the conclusions of previous studies, despite of differences in population, screening methods, currencies, and particularly due the use of a hs-cTnT assay. This suggests that there may be a reasonable cost-effectiveness benefit with hs-cTnT screening after noncardiac surgery. In comparison with previous studies, our innovation was to use a systematic cTn screening with a high-sensitivity method that has been demonstrated to improve by nearly fivefold the postoperative myocardial injury detection rate of the nonhigh sensitivity methods.[23]

Limitations and strengths

Our study has limitations. Firstly, we did not have a cohort of usual care, so we used a hypothetical reference cohort. Patients of the usual care strategy were the same as those in the systematic hs-cTnT screening group, but studied as if they were managed based on local clinical practice and on the available data from the literature.[14] Secondly, our model was structured as a short-term (30-day follow-up) analysis and we lacked data on longer follow-up. Thirdly, there were no other studies providing specific value(s) for the WTP per a PMI; therefore, we have only analysed different WTP values for better understanding of the results of our probabilistic sensitivity analysis through the evolution of the CEAC. Fourthly, we did not assess quality-adjusted life years (QALYs) for each of the assessed strategies. Finally, our study was based on the costs of personnel, drugs, hospital stay, etc. from the Spanish national health system; therefore, our costs could be different, usually lower, than those of other settings.

Our study has also some strengths. Firstly, to our knowledge, this is the first cost-effectiveness study comparing a systematic hs-cTnT assay-based strategy in high-risk patients, undergoing noncardiac surgery. Secondly, we obtained an estimation of the cost per any additional detected PMI. Finally, the hs-cTnT assay used in our study is more sensitive and accurate at detecting low concentrations, contributing to the higher detection rate of PMI, compared with contemporary cTn assays used in previous studies.

Implications for practice and research

Early detection of PMI may contribute to improve its management, even if more expensive than usual care. Our effectiveness endpoint was PMI detection. Despite no evidence to date that detecting myocardial injury reduces the incidence of hard endpoints (e.g., mortality), detection of postoperative complications, such as PMI, may contribute to improve prognosis of these patients. Patients with PMI in our study were submitted for additional evaluations, some of them receiving pharmacological treatments or further procedures, that have proved to be effective reducing severe cardiovascular complications, including mortality.[8] Results of our study may be useful for clinical practice and decision makers when deciding to implement systematic hs-cTnT screening programs in peri-operative settings. They also can be useful for future economic evaluations, especially in countries with similar healthcare characteristics.

Conclusion

The results of our study support the importance of systematic peri-operative hs-cTn screening in high-risk noncardiac surgery patients, and suggest that it is a cost-effective strategy. However, economic evaluations including a long-term horizon are still needed.

Acknowledgements relating to this article

Assistance with the study: we would like to thank all the patients that agreed to be included in the study and to all the personnel of our hospital that participated in its different steps. Thanks to the personnel of Department of Economics and Centre de Recerca en Economia i Sostenibilitat (ECO-SOS), Universitat Rovira i Virgili, Spain.

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Conflict of interest: none.

Presentation: preliminary data of this study were presented as a poster presentation at the Peri-operative Care Congress, November 11–14, 2021, Toronto, Canada.

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Disclaimer: the funders had no role in the study design, data collection, management, analysis, writing of the report, the decision to submit the report for publication, and they will not have ultimate authority over any of these activities.

Data availability statement: any data required to support the study can be supplied upon reasonable request. The data used in the present study is part of a larger dataset. The data not used for this manuscript will be employed in future manuscripts. Technical appendix, statistical code, and dataset available from the Dryad repository.

This manuscript was handled by Dan Longrois.

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Erratum

Cost-effectiveness of a high-sensitivity cardiac troponin T systematic screening strategy compared with usual care to identify patients with peri-operative myocardial injury after major noncardiac surgery: erratum

Due to an error at the Publisher's office, key information was missing from the Acknowledgements in the article, "Cost-effectiveness of a high-sensitivity cardiac troponin T systematic screening strategy compared with usual care to identify patients with peri-operative myocardial injury after major noncardiac surgery".[1]

The full list of Acknowledgements is provided below:

Authors' contributions:

Ekaterine Popova (EP): Conceptualization, methodology, data curation, investigation, writing – original draft, visualisation, project administration. **Pablo Alonso-Coello (PAC)**: Conceptualization, methodology, writing – review & editing, supervision, funding acquisition. **Jesús Alvarez-Garcia (JAG):** Methodology, data curation, project administration, visualisation, writing, review & editing. **Pilar Paniagua-Iglesias (PPI):** Methodology, data curation, project administration, writing – review & editing. **Montserrat Rué-Monné (MRM):** Conceptualization, writing – review & editing. **Miguel Vives- Borrás (MVB):** Project administration, data curation, visualisation, writing – review & editing. **Adria Font-Gual (AFG):** Project administration, data curation, visualisation, writing – review & editing. **Ignasi Gich-Saladich (IGS):** Formal analysis, writing – review & editing. **Cecilia Martinez Bru (CMB):** Project administration, visualisation, writing – review & editing. Supervision, **Jordi Ordoñez-Llanos (JOL):** Conceptualization, writing – review & editing. **Misericordia Carles-Lavila (MCL)**: Conceptualization, methodology, formal analysis, data curation, visualisation, writing – review & editing, supervision.

Acknowledgements relating to this article

Assistance with the study: we would like to thank all the patients that agreed to be included in the study and to all the personnel of our hospital that participated in its different steps. Thanks to the personnel of Department of Economics and Centre de Recerca en Economia i Sostenibilitat (ECO-SOS), Universitat Rovira i Virgili, Spain.

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Data availability statement: any data required to support the study can be supplied upon reasonable request. The data used in the present study is part of a larger dataset. The data not used for this manuscript will be employed in future manuscripts. Technical appendix, statistical code, and dataset available from the Dryad repository.

The record is hereby corrected.

Reference

1 Popova E, Alonso-Coello P, Álvarez-Garcia J, *et al*. Cost-effectiveness of a high-sensitivity cardiac troponin T systematic screening strategy compared with usual care to identify patients with peri-operative myocardial injury after major noncardiac surgery. *Eur J Anaesthesiol* 2023; **40**:179–189.

DOI:10.1097/EJA.0000000000001893

4.3. ESTUDIO III. Lesión miocárdica tras cirugía mayor no cardiaca evaluada con imagen cardiaca avanzada: un estudio piloto

Título	**Myocardial injury after major non-cardiac surgery evaluated with advanced cardiac imaging: a pilot study**
Referencia	Álvarez-García J, Popova E, Vives-Borrás M, de Nadal M, Ordóñez-Llanos J, Rivas-Lasarte M, Moustafa AH, Solé-González E, Paniagua-Iglesias P, García-Moll X, Viladés-Medel D, Leta-Petracca R, Oristrell G, Zamora J, Ferreira-González I, Alonso-Coello P, Carreras-Costa F. BMC Cardiovasc Disord. 2023 Feb 10;23(1):78. DOI: 10.1186/s12872-023-03065-6. PMID: 36765313; PMCID: PMC9911951.
Factor de impacto	2,1
Cuartil	Q 3
Categoría	Cardiac & Cardiovascular Systems

4.3.1. Resumen de resultados del tercer estudio

- *Población del estudio*

De un total de 373 pacientes con LMP detectados entre los dos hospitales participantes, 58 no cumplieron los criterios de inclusión, otros 192 declinaron su participación, 5 se retiraron del estudio después de haber dado su consentimiento y, finalmente, 66 no se incluyeron debido a problemas logísticos como altas hospitalarias tempranas, falta de disponibilidad de la TCC, fragilidad de los pacientes y dificultades con el desplazamiento para visitas adicionales. Después de estas exclusiones, finalmente se logró incluir a 52 pacientes en el grupo de LMP. Se ha de reseñar que muchos pacientes declinaron su participación en el estudio porque requería su desplazamiento tras el alta, desde su domicilio en su lugar de residencia al centro de obtención de las imágenes.

En cuanto al grupo de control, debido al elevado número de pacientes elegibles (n=1972) para alcanzar los cálculos de tamaño muestral, inicialmente se propuso incluir el mismo número de pacientes que presentaban LMP. Sin embargo, la tasa de participación en este grupo fue aún más baja debido al gran número de pacientes que se negaron a participar, en parte debido a los mismos problemas logísticos mencionados anteriormente, así como por la reticencia a someterse a pruebas adicionales sin existir una justificación clínica que dictara su necesidad.

- *Características de los casos de LMP y pacientes control*

La mayoría de los pacientes (n=58; 90,6%) tenían más de 65 años (edad media 75,1 años), y algo menos de la mitad (46,9%) eran mujeres. Se observó una elevada prevalencia de factores de riesgo CV como HTA (70,3%), DM (37,5%) y dislipidemia (51,5%), y, en consecuencia, los pacientes estaban en tratamiento con IECAs (55,6%), estatinas (46,0%) y aspirina (33,3%). También presentaron frecuentemente arteriopatías periféricas (14,1%) o enfermedad pulmonar obstructiva crónica (15,6%).

No se observaron diferencias relevantes en las características basales de los pacientes entre los grupos de LMP y control, aunque la DM fue más frecuente, aunque no significativamente, en los pacientes con LMP (42,3% vs. 16,7% p=0,184). En cuanto a la evaluación de riesgo según el IRCR, once de los 12 (91,7%) de los sujetos control presentaron el índice mínimo, mientras que en los pacientes con LMP esta proporción fue significativamente menor (59,6%, p=0,01). No se observaron diferencias en los valores de TncT-as preoperatorios entre pacientes con LMP y controles. Sin embargo, en los postoperatorios el grupo LMP mostró valores de TncT-as de 2 a 3 veces más elevados en comparación con los controles (41 vs. 14 ng/L, p<0,002 y 31 vs. 11 ng/L, p<0,001), a las 48 h y 72 h, respectivamente.

Durante la cirugía, la hipotensión arterial se observó con mayor frecuencia en pacientes con LMP (83,3% vs. 65,3%), especialmente la que requirió tratamiento con vasopresores (90,0% vs. 71,0%), aunque las diferencias no alcanzaron significación estadística. En el grupo de pacientes con LMP también se observó la existencia de sangrado intraoperatorio (10,4%) y shock intra (16%) y postoperatorio (10%), frente a su ausencia en el grupo control. Desafortunadamente, debido al limitado número de pacientes, especialmente controles, estas diferencias no fueron estadísticamente significativas.

- *Resultados de las pruebas avanzadas de imagen cardiaca*

En todos los 64 pacientes (100%) del grupo del estudio (LMP y controles) se realizó un ecocardiograma, un TCC en el 97% y una RMC en el 77%. La mediana de la fracción de eyección ventricular izquierda (FEVI), medida mediante ecocardiograma, fue normal en ambos grupos, y solo se observó movilidad anormal de la pared cardíaca en un 5,8% de los casos con LMP. Un total de 19 pacientes de ambos grupos presentaron enfermedad arterial coronaria (EAC) significativa (clasificada como *CAD-RADS ≥3*); la frecuencia de esta fue similar en ambos grupos (30% en el grupo LMP; 33% en el grupo control). Se observaron placas ateromatosas calcificadas en aproximadamente dos tercios de los pacientes de ambos grupos (58,0% en LMP, 58,3% en controles). Solo se observaron placas vulnerables en tres pacientes (uno control y dos con LMP).

En las exploraciones por RMC, la FEVI y el movimiento anormal de la pared fueron similares a los detectados por la TCC. El realce tardío de gadolinio (RTG) se observó en casi un tercio de los pacientes

con LMP (28,2%) y en los controles sin LMP (30,3%). Se realizó una prueba de estrés con adenosina en los 19 pacientes con una EAC significativa. No se observaron diferencias entre los grupos en la frecuencia de anomalías de la perfusión mural, al igual que en las exploraciones ecocardiográficas o de RMC; pero en los pacientes con LMP se objetivaron patrones isquémicos cardíacos en cinco casos y segmentos isquémicos en dos casos, en comparación con su inexistencia en el grupo control.

- *Resultados de seguimiento*

En el seguimiento de un año, tanto las CCVM, así como la mortalidad por cualquier causa, 15,4% y 7,7% respectivamente, únicamente ocurrieron en los pacientes con LMP. De las cuatro muertes registradas, una se catalogó como muerte súbita cardíaca y ocurrió en un paciente con múltiples factores de riesgo CV, mientras que las otras tres muertes restantes se debieron a progresión de las neoplasias.

Tres pacientes con LMP presentaron síntomas isquémicos durante el seguimiento y dos de ellos fueron sometidos a revascularización cardiaca sin complicaciones, revelando una enfermedad arterial coronaria significativa. El tercer paciente recibió tratamiento médico, ya que su mayor fragilidad desaconsejaba la intervención, según el criterio de su equipo responsable.

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Myocardial injury after major non-cardiac surgery evaluated with advanced cardiac imaging: a pilot study

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Abstract

Background Myocardial injury after non-cardiac surgery (MINS) is a frequent complication caused by cardiac and non-cardiac pathophysiological mechanisms, but often it is subclinical. MINS is associated with increased morbidity and mortality, justifying the need to its diagnose and the investigation of their causes for its potential prevention.

Methods Prospective, observational, pilot study, aiming to detect MINS, its relationship with silent coronary artery disease and its effect on future adverse outcomes in patients undergoing major non-cardiac surgery and without postoperative signs or symptoms of myocardial ischemia. MINS was defined by a high-sensitive cardiac troponin T (hs-cTnT) concentration > 14 ng/L at 48–72 h after surgery and exceeding by 50% the preoperative value; controls were the operated patients without MINS. Within 1-month after discharge, cardiac computed tomography angiography (CCTA) and magnetic resonance imaging (MRI) studies were performed in MINS and control subjects. Significant coronary artery disease (CAD) was defined by a CAD-RADS category ≥ 3. The primary outcomes were prevalence of CAD among MINS and controls and incidence of major cardiovascular events (MACE) at 1-year after surgery. Secondary outcomes were the incidence of individual MACE components and mortality.

Results We included 52 MINS and 12 controls. The small number of included patients could be attributed to the study design complexity and the dates of later follow-ups (amid COVID-19 waves). Significant CAD by CCTA was equally found in 20 MINS and controls (30% vs 33%, respectively). Ischemic patterns (n = 5) and ischemic segments (n = 2) depicted by cardiac MRI were only observed in patients with MINS. One-year MACE were also only observed in MINS patients (15.4%).

Conclusion This study with advanced imaging methods found a similar CAD frequency in MINS and control patients, but that cardiac ischemic findings by MRI and worse prognosis were only observed in MINS patients. Our results,

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obtained in a pilot study, suggest the need of further, extended studies that screened systematically MINS and evaluated its relationship with cardiac ischemia and poor outcomes.

Trial registration Clinicaltrials.gov identifier: NCT03438448 (19/02/2018).

Keywords Myocardial injury, Noncardiac surgery, Cardiac imaging, Pathophysiology

Introduction

Annually, over 300 million people undergo major noncardiac surgery worldwide [1]. Despite preoperative screening, surgical improvements and increased patient monitoring, myocardial infarction remains the first cardiovascular cause of morbidity and mortality within 30 days after surgery [2]. Atherothrombosis is the underlying cause for most non-operative myocardial infarctions; but the mechanisms of the myocardial injury in noncardiac surgery (MINS), including perioperative myocardial infarction, are multiple and difficult to identify in the usual clinical practice. Theoretically, myocardial injury may be caused by four distinct mechanisms: coronary plaque rupture [3, 4], myocardial oxygen supply–demand mismatch [5, 6], non-ischemic cardiac disorders, such an atrial fibrillation episode [7], or non-cardiac causes, such as pulmonary embolism [8]. However, the angiographic, histological, or imaging studies required to identify all the MINS etiological mechanisms of are difficult to be implemented in all patients undergoing non-cardiac surgery [9]. Better understanding of causes originating MINS could help to develop potential preventive and therapeutic interventions. Recently, cardiac computed tomography angiography (CCTA), has demonstrated to improve the value of revised cardiac risk index [10], an established prognostic indicator of major cardiac events after surgery [11]. Moreover, cardiac magnetic resonance imaging (MRI) is considered the gold standard for non-invasively study of myocardial functionality. Therefore, minimally invasive diagnostic tests, like CCTA and cardiac MRI, could be promising tools to identify the occurrence and elucidate the underlying mechanisms of MINS.

In this pilot study, we aimed to identify with CCTA and MRI the existence of non-clinically evident coronary artery disease (CAD) and/or focal myocardial fibrosis in patients with or without MINS after undergoing major non-cardiac surgery. In addition, we aimed to analyse the relationship between MINS occurrence and the future major cardiovascular events (MACE). The primary outcomes were prevalence of CAD among MINS and controls and incidence of MACE at 1-year. Secondary outcomes were incidence of all 1-year outcomes, including mortality and individual components of MACE.

Methods

We adhered to the STROBE reporting guidelines (Additional file 1: Table S1). The protocol and the informed consent for troponin sampling and cardiac image studies were approved by the Ethics Committee of Clinical Research of the Hospital de la Santa Creu i Sant Pau in May 11th, 2016. The other participating centre (Hospital Vall d´Hebron) adhered to this approval (permitted by our local legislation) and used the same informed consents. The study was registered at Clinicaltrials.gov (NCT03438448). All participants provided written informed consent before recruitment.

Study design

The current was a prospective, observational, cohort study in patients undergoing major noncardiac (elective or urgent) surgery (mainly digestive, gynaecologic, neurosurgery, orthopaedic, otorhinolaryngologic, plastic, thoracic, traumatological and vascular), requiring at least an overnight hospital admission. The study was carried out in two University Spanish hospitals, between July 2016 and December 2019. In the one of the participating centres (Hospital de la Santa Creu i Sant Pau) the current study was one of the sub-studies of a large cohort study aiming to evaluate the feasibility and impact of implementation of the systematic preoperative and postoperative hs-cTnT screening, as well as its cost-effectiveness., where systematic hs-cTnT screening program for MINS, was implemented at the routine perioperative care. Therefore, all patients provided informed consent for troponin sampling before surgery. In the other centre (Hospital Vall d´Hebron), where hs-cTnT screening was not performed systematically, the samplings were included in the framework of the study using the same informed consent for troponin sampling before surgery. All included patients at the cardiac imaging study, from two participating centres were identified and invited to participate after surgery and provided their specific imaging study informed consent.

Study participants

The study was focused on acute postoperative myocardial injury, i.e., MINS (excluding myocardial infarction). All patients had to meet at least one of the following inclusion criteria: (1) age $\geq$ 65 years old, (2) antecedents of stroke or transient ischemic attack or peripheral vascular

disease if < 65 years old, or (3) preoperative estimated glomerular filtration rate (eGFR) between 30–59 mL/min/1.73 m^2 Exclusion criteria included: (1) antecedents of ischemic heart disease and/or chronic heart failure, and (2) any contraindication to perform cardiac CCTA or MRI. Patients fulfilling inclusion criteria were identified by research personnel at post-surgery units, invited to participate in the image study and those accepting to be included signed a specific informed consent.

Hs-cTnT measurements

In the included patients, we measured the high-sensitive cardiac Troponin T (hs-cTnT, Roche Diagnostics, Basel, Switzerland) at three times: preoperatively and 48 and 72 h after surgery. The values of the limit of detection, 99th upper reference percentile (URL) and 10% coefficient of variation were 5.0 ng/L, 14.0 ng/L (both sexes) and 13.0 ng/L, respectively.

MINS definition and management

When a postoperative rise and/or fall pattern in hs-cTnT, with at least one value above the URL, was detected in a patient a 12-lead electrocardiogram (ECG) was performed. If the postoperative ECG showed changes vs the ECG before surgery, an echocardiography was conducted to rule out wall motion abnormalities. After completing the process, MINS was defined as any postoperative hs-cTnT value higher than the URL and showing at least a 50% increase respect to the preoperative concentration, in a patient without ECG signs or symptoms of myocardial ischemia. The control group included the patients without hs-cTnT elevations. A structured cardiology consultation was performed in MINS and control groups.

Advanced cardiac imaging studies (CCTA and cardiac MRI)

CCTA and MRI were performed in all patients within the first month after discharge and at the same centre (Hospital de Sant Pau, who acted as core-lab for cardiac imaging). On the previous days of the CCTA, patients were treated with a beta-blocker (atenolol 25–50 mg or ivabradine 5–7.5 mg to achieve a heart rate ≤ 60 beats per minute). A pair of expert evaluators formed by a cardiologist and a radiologist with level 3 training in interpretation of CCTA, read each angiogram using a 17-segment model of the coronary arteries without knowledge of the clinical data. Per-patient anatomical severity was classified according to the Coronary Artery Disease—Reporting and Data System (CAD-RADS) [12]. Triple-rule-out CCTA examinations (coronary artery disease, pulmonary embolism, and acute aortic pathology) were also performed. After the CCTA study, an MRI exam was performed to evaluate the global and segmental cardiac contractility and presence of focal fibrosis, using late gadolinium enhancement (LGE) contrast. We classified the LGE pattern as "ischemic" if subendocardial or transmural delayed contrast enhancement in a vascular distribution was observed and "non-ischemic" if enhancement was distributed patchy or diffuse, not following a vascular territory, mainly in mesocardial or epicardial locations [13]. Finally, in those with significant CAD in the CCTA (CAD-RADS ≥ 3), a pharmacological stress with adenosine was conducted, to assess functional impact of each coronary stenosis. A more detailed version of the study protocol was previously published [14].

Follow-up and data collection

All patients were followed for the study outcomes at 1 month, and at 1 year, after the date of surgery. The follow-up visits were conducted by telephone, supported by clinical electronic records. If the patients (or relatives) indicated that they had experienced any of the main outcomes, we obtained the relevant source documents from the corresponding electronic health records. All variables including risk factors (including the Revised Cardiac Risk Index-RCRI- [15]), comorbidities, medical treatment, and perioperative data (intraoperative hypotension was defined as a 30% drop of systolic blood pressure from baseline, intra and postoperative bleeding were defined as a 30 g/L drop from preoperative haemoglobin, need for transfusion or requiring haemostatic surgery, and intra and postoperative shock) were collected by study personnel on case report forms and entered at secure online database (www.clinapsis.com).

Main outcomes

The primary outcomes were prevalence of CAD among MINS and no-MINS patients and incidence of MACE at 1-year. MACE was defined as a composite of myocardial infarction, unstable angina, need of cardiac revascularization, heart failure, new atrial fibrillation episode, stroke, or pulmonary embolism (according definitions of the most recent guidelines). All-cause death was also registered. Secondary outcomes were incidence of all 1-year outcomes, including mortality and individual components of MACE.

Statistical considerations

Sample size

In the original protocol of this cardiac imaging sub-study, it was estimated that it would be necessary to recruit 260 participants (130 MINS cases and 130 matched controls) to detect an association between MINS condition and significant coronary atherosclerosis.

To calculate these sample sizes, we assume a prevalence of significant coronary atherosclerosis of around 19% in our high-risk population. The prevalence data was based

in a previous study [16] of some of the current co-authors in a similar population to that of the study.

Statistical analysis

For categorical variables, the percentage and the number of cases and the mean and standard deviation or median and interquartile range for quantitative variables were provided. Comparisons between groups were assessed with the Student's T test or the Mann–Whitney's U-test for continuous variables and with the chi-square tests or the Fisher exact test for comparing the proportions of categorical variables. Two-sided significance levels of 0.05 were used in all analyses. Data were analysed using STATA SE Version 13.0 (StataCorp LLC, College Station, TX, USA).

Results

Clinical characteristics of the study population and risk assessment of index surgery

From total 373 screened MINS patients, 58 did not fulfilled inclusion criteria, other 192 declined to participate, additional 5 withdrawn from the study after had provided informed consent, and finally, 66 were not included due to logistic issues (discharged before complete sampling, CCTA not available, frailty). Therefore, we included 52 MINS patients and completed their follow-up. Regarding the control group and owing to the large number of eligible patients (1,972), we proposed to participate to a similar number no-MINS patients as the needed to achieve our previous size calculations. Unfortunately, in this group we obtained even lower participation rate than in MINS, mainly due to the same reasons as in the MINS group plus a huge number of refusals. We could only include and complete the follow-up in 12 controls. In the recruiting centre with a systematic MINS screening a 10.5% of screened patients were lost by lack on hs-cTnT value at 72 h after surgery. The 1-year follow-up of several cases coincide with the first and second COVID-19 waves in Spain; thus, an indeterminate number of missed follow-ups, particularly in control subjects (no-MINS), could be attributed to the inability of some elderly, frail patients to answer to the follow-up request due to their current clinical condition. Most patients (58, 90.6%) were ≥ 65 years old (mean age 75.1), 30 (46.9%) were females, all Caucasians, with a high prevalence of cardiovascular risk factors mainly hypertension, diabetes mellitus and different dyslipidaemias, and, accordingly, on current treatment with antihypertensive drugs, statins, and aspirin. Peripheral artery disease and chronic obstructive pulmonary disease were also frequent (~15%). There were no relevant differences in the baseline features of patients between MINS and control groups, though diabetes mellitus was found in 42.3% (22) of MINS patients and in 16.7% (2) of controls (Table 1).

Regarding risk assessment prior to index surgery, the RCRI class I was separately analysed from the other classes, since it was the most frequently observed among the patients, to try to avoid that a difference on risk assessment between MINS and controls could remain «unseen» in the general statistical assessment of the fourth RCRI groups. Low RCRI was more frequent in controls (11, 91.7%) than in MINS patients (31, 59.6%, $p < 0.01$); eGFR was lower, in patients with MINS than in controls (71.1 vs. 76.5 mL/min/1.73 m^2) though the difference was not statistically significant ($p = 0.136$) (Table 2). Hs-cTnT concentrations were not different between MINS and controls previously to surgery, but the MINS group showed median values two to three times higher than controls at 48 h (41 vs 14 ng/L,

Table 1 Preoperative clinical characteristics of the study population

	Total (64)	Patients with MINS (52; 81.2%)	Controls* (12; 18.8%)	*P* value
Age, years	75.1 [9.3]	75.2 [9.9]	74.5 [6.2]	0.762
≥ 65 years	58 (90.6)	47 (90.4)	11 (91.7)	0.891
Female sex	30 (46.9)	24 (46.2)	6 (50.0)	0.810
Body mass index (kg/m^2)	22.3 [3.5]	22.0 [3.7]	23.5 [2.5]	0.109
Stroke	5 (7.8)	4 (7.7)	1 (8.3)	0.941
Transient ischemic attack	1 (1.6)	1 (1.9)	0 (0)	1.000
Peripheral artery disease	9 (14.1)	8 (15.4)	1 (8.3)	1.000
Hypertension	45 (70.3)	37 (71.2)	8 (66.7)	0.759
Diabetes mellitus	24 (37.5)	22 (42.3)	2 (16.7)	0.184
Dyslipidaemia	33 (51.6)	25 (48.1)	8 (66.7)	0.245
COPD	10 (15.6)	9 (17.3)	1 (8.3)	0.672
Chronic kidney disease	8 (12.5)	8 (15.4)	0 (0)	1.000
Deep vein thrombosis	1 (1.6)	0 (0)	1 (8.3)	1.000
Treatments				
ASA	21 (33.3)	19 (36.5)	2 (16.6)	0.310
Statins	29 (46.0)	23 (44.2)	6 (50.0)	0.533
Oral anticoagulants	4 (6.4)	3 (5.8)	1 (8.3)	0.546
Beta-blockers	4 (6.4)	3 (5.8)	1 (8.3)	0.546
ACEI	35 (55.6)	30 (57.7)	5 (41.7)	0.458

Data are expressed as: number (%), mean [standard deviation], or median (interquartile range) value, as appropriate

MINS: myocardial injury in non-cardiac surgery; COPD: chronic obstructive pulmonary disease; ASA: acetylsalicylic acid; ACEI: angiotensin-converter enzyme inhibitors

*Controls = patients without MINS

Table 2 Values of the Revised Cardiac Risk Index (RCRI) of index surgery and peri and postoperative complications in patients with MINS and controls

	MINS (52; 81.2%)	Controls (12; 18.8%)	*P* value
RCRI			
I	31 (59.6)	11 (91.7)	0.01
II	15 (28.9)	1 (8.3)	1.000
III	2 (9.6)	0 (0)	1.000
IV	1 (1.9)	0 (0)	1.000
Preoperative BP (mm Hg)			
Systolic	134 (124–146)	138 (119–159)	0.727
Diastolic	71 (60–83)	79 (70–86)	0.207
Preoperative HR (bpm)	74 (63–80)	70 (64–76)	0.534
Preoperative haemoglobin (g/L)			
≤ 100	3 (5.8)	1 (9.0)	0.670
101–129	28 (53.9)	5 (45.5)	
≥ 130	21 (40.3)	5 (45.5)	
eGFR (mL/min/1.73 m^2)	71.1 [16.7]	76.5 [9.0]	0.136
Hs-cTnT (ng/L)			
Preoperative	11 (9–16)	11 (8–12)	0.284
48 h post-surgery	41 (23–73)	14 (11–32)	0.002
72 h post-surgery	31 (18–48)	11 (10–13)	0.001
Priority of surgery			
Elective	43 (82.7)	8 (66.7)	0.243
Urgent	9 (17.3)	4 (33.3)	
Type of surgery			
Orthopaedic	22 (42.3)	8 (66.7)	
General (Digestive)	17 (32.7)	2 (16.7)	
Vascular	7 (13.5)	1 (8.3)	
Neurosurgery	1 (1.9)	1 (8.3)	
Thoracic	4 (7.7)	0 (0)	
Others	1 (1.9)	0 (0)	0.451
Intraoperative hypotension	32 (65.3)	10 (83.3)	0.309
*Requiring treatment***	22 (71.0)	9 (90.0)	0.402
Bleeding			
Intraoperative	5 (10.4)	0 (0)	1.000
Postoperative	9 (18.0)	2 (18.2)	1.000
Shock			
Intraoperative	8 (16.0)	0 (0)	1.000
Postoperative	5 (10.0)	0 (0)	1.000
Ischemic symptoms or signs like ECG	3 (5.8)	0 (0)	1.000

Data are expressed as: number (%), mean [standard deviation], or median (interquartile range) value, as appropriate

MINS: myocardial injury in non-cardiac surgery; Controls: patients without MINS; RCRI: revised cardiac risk index; BP: blood pressure; HR: heart rate; bpm: beats per minute; eGFR: estimated glomerular filtration rate according to CKD-EPI equation; mL: millilitre; min: minute; m: meter; hs-cTnT: high-sensitive cardiac troponin T; ng: nanogram; L: litter; h: hour

*Controls = Patients without MINS

**Inotropic or vasopressor therapy required

$p < 0.002$) and 72 h (31 vs 11 ng/L, $p < 0.001$) of surgery. During intervention, hypotension was frequent in MINS and controls (65.3% and 83.3%, respectively) requiring therapy in most cases (71.0% and 90.0%, respectively). In the MINS group, intraoperative bleeding (10.4%) and intra and postoperative shock (16% and 10%, respectively) were found compared with their complete absence in the control group, though owing the few cases the differences between groups did not reach statistical significance.

Advanced cardiac imaging findings

Out of 64 patients, we performed an echocardiogram, a CCTA scan, and a cardiac MRI in 64 (100%), 62 (97%), and 49 (77%), respectively. Table 3 describes the main findings of the advanced cardiac imaging studies. The median left ventricular ejection fraction (LVEF) measured by echocardiogram was normal in both groups, and abnormal wall motion was observed only in three MINS patients. The frequency of significant CAD (CAD-RADS ≥ 3) was similar in MINS (n = 15, 30%) than in the control group (n = 4, 33%); a total of nineteen subjects of both groups had a CAD-RADS ≥ 3. Calcified plaques were found in approximately two thirds of patients of both groups (29 MINS: 58.0%, 7 controls: 58.3%); vulnerable plaques were quite infrequent. In the MRI explorations, LVEF and abnormal wall motion findings were similar than those of CCTA. Late gadolinium enhancement (LGE) was similarly found in near to one third of MINS (n = 11, 28.2%) and controls (n = 3, 30.3%). An adenosine test was performed in the nineteen subjects with a significant CAD by the CAD-RADS index. No differences were observed between groups in the frequency of abnormalities of wall perfusion, as it was found in the echocardiographic or MRI explorations; we found cardiac ischemic patterns in five and ischemic segments in two MINS patients compared with any in the control group.

Table 3 Findings in advanced cardiac imaging in patients with MINS and controls

	MINS	Controls	*P* value
Echocardiography (n = 62)	**52 (100%)**	**12 (100%)**	–
LVEF, %	65 (60–65)	63 (60–65)	0.733
Abnormal wall motion	3 (5.8)	0 (0)	1.000
CCTA (n = 62)	**50 (96.2%)**	**12 (100%)**	–
Agatston score	143 (0–600)	128 (0–583)	0.889
CAD-RADS 0	11 (22.0)	1 (8.3)	0.833
CAD-RADS 1–2	24 (48.0)	7 (58.3)	
CAD-RADS 3	10 (20.0)	3 (25.0)	
CAD-RADS 4–5	5 (10.0)	1 (8.3)	
Calcified plaque	29 (58.0)	7 (58.3)	0.983
Vulnerable plaque	2 (4.0)	1 (8.3)	0.482
Cardiac MRI (n = 49)	**39 (75.0)**	**10 (83.3)**	–
LVEF, %	63 (7)	64 (4)	0.563
Abnormal wall motion	1 (2.6)	1 (10.0)	0.370
LGE positive	11 (28.2)	3 (30)	1.000
Ischemic pattern	5 (45.5)	0 (0)	1.000
Microvascular obstruction	2 (5.1)	0 (0)	1.000
Abnormal wall perfusion**	4 (26.7)	1 (25.0)	1.000
Ischemic segments**	2 [0–5]	0 [0–0]	1.000
Mod-severe PIQS score**	1 (0–1)	0 (0–0)	1.000

Bold values indicate number of subjects in each group

Data are expressed as: number (%), mean [standard deviation], or median (interquartile range) value, as appropriate

MINS: myocardial injury in non-cardiac surgery; LVEF: left ventricular ejection fraction; CCTA: cardiac computed tomography angiography; CAD: coronary artery disease; MRI: magnetic resonance imaging; LGE: late gadolinium enhancement; PIQS: perfusion index quantitative score

*Controls = patients without MINS

**Adenosine test performed only in those patients with CAD-RADS (Coronary Artery Disease-Reporting and Data System) ≥ 3 (N = 19)

Outcomes in the follow-up

All cause-mortality (4 patients, 7.7% after 1-year follow-up) only occurred in the MINS group; a sudden cardiac death happened in a patient with many treated cardiovascular risk factors and the other deaths were due to malignancies. MACE was also only detected in MINS patients (n = 8, 15.4%) (Table 4). Three patients with MINS developed ischemic symptoms; two of them undergone coronary angiography, which showed significant coronary artery disease. Both patients were revascularized during the procedure without further complications. The third patient with ischemic symptoms was managed with medical treatment, because due to his/her fragility a coronary interventionism was discouraged.

Discussion

In the current study, conducted in a group of patients with high cardiovascular risk undergoing major non-cardiac surgery, we have analysed the frequency of myocardial injury (MINS) detected with high-sensitive troponin T (hs-cTnT), the occurrence of subclinical coronary artery disease (CAD) detected with advanced imaging techniques, and the occurrence of cardiovascular complications after one year follow-up.

Table 4 One-year outcomes in patients with MINS and controls

	MINS (52; 81.2%)	Controls (12; 18.8%)
All-cause mortality	4 (7.7)	0
MACE	8 (15.4)	0
Unstable angina	3 (5.8)	0
Myocardial infarction	0	0
Cardiac revascularization	2 (3.9)	0
Heart failure	0	0
New atrial fibrillation	2 (3.9)	0
Stroke	1 (1.9)	0
Pulmonary embolism	0	0

Data are expressed as number (%), mean (standard deviation), or median (interquartile range), as appropriate

MINS: myocardial injury in non-cardiac surgery; MACE: major adverse cardiovascular events

*Controls = Patients without MINS

We found several interesting findings. First, the Revised Cardiac Risk Index (RCRI) stage I, associated to the lowest cardiac risk, was significantly more frequent in control subjects than in MINS patients. Though differences in the preoperative variables included in the RCRI between both groups did not achieve statistical significance, MINS patients received more often thoracic, abdominal, and vascular surgeries and have an eGFR lower than controls; taking together, all these differences could justify the predominance of a RCRI value associated to low cardiac risk in the control population. Second, in our study, we measured hs-cTnT pre and postoperatively and MINS was defined by percentual increases against the preoperative concentration. In the MINS group, the postsurgical hs-cTnT concentrations were only mildly elevated (2–3 times) over the upper reference limit (URL) of 14 ng/L, but between 3 to 4-times over the preoperative values. This result support that the extent of myocardial injury in the MINS group was small and that it was easier to detect by hs-cTnT serial changes rather than by reference to the URL. Our findings agree with the low individuality index of hs-cTnT observed in different studies both in control subjects and in patients with cardiac or renal disease [17]. When the individuality index of a variable is low, the signification of its value must be analysed against its serial evolution rather than against its URL. Moreover, patients as those included in our study often have basal hs-cTnT values higher than the URL; thus, to define an ongoing myocardial injury serial values and significant changes are required [18]. Third, by CCTA we found that significant CAD, measured as a CAD-RADS $\geq$ 3.0, existed in 30% of MINS and in 33.3% of controls; these findings superseded the assumptions made in our protocol. Our results agreed with those of OPTIMUS [19] and CORONARY Vision-CTA [11] studies, which observed that atherothrombosis was implicated in one third of cases of cardiac damage in non-cardiac surgery patients. However, as outlined in a sub-study of the CORONARY Vision-CTA study, many patients with severe coronary lesions in the CCTA did not have postoperative complications suggesting that CCTA could overestimate the future risk of these patients. The authors of the study suggested that MRI could improve the identification of patients at risk of postoperative outcomes [20]. Of note, the CCTA explorations in the CORONARY Vision-CTA were performed preoperatively and, in our study, postoperatively. Fourth, by late gadolinium enhanced cardiac MRI, we identified focal fibrosis, a sign of myocardial ischemia, in one-third of both MINS patients and controls. Our population, although exclude patients with previous ischemic cardiac disease or chronic heart failure, included many subjects with cardiovascular risk factors or antecedents of cerebrovascular and peripheral arterial diseases. Thus, our patients would be prone to have subclinical myocardial ischemic features in MRI; same MRI findings have been observed in large studies in asymptomatic individuals or general population presenting similar health status than our patients [21, 22],. There are only one study using MRI to detect postoperative myocardial injury after non-cardiac surgery in 22 patients with an age and health status similar to ours and with significative CAD detected by CCTA, although myocardial injury was assigned using a contemporary cardiac troponin I assay with lower analytical and clinical sensitivity than high sensitive assays used in our study [23]. The study found clinically silent pulmonary embolism in one-third of patients with myocardial injury, an alteration that we did not observe in our study. Late gadolinium enhancement and perfusion defect were observed in one-third of cases, same proportion as in our study. The small number of included patients in the referred study and in own study could be the cause of highly discrepant proportions, but really derived from very small numbers. Fifth, adenosine stimulation, only conducted in patients with a CAD-RADS $\geq$ 3.0, revealed that unlike the similar frequency of the index and abnormal wall reperfusion defects in both MINS and controls, only MINS group had ischemic segments in MRI. Pharmacological stress perfusion with adenosine is the non-invasive investigation of choice in patients with suspected, but uncertain myocardial ischemia diagnosis [24]. As mentioned, our patients, both those with MINS and those without, have an increased preoperatory risk of cardiovascular complications. However, despite the similarities between both groups in some cardiac postoperative image features, the adenosine stimulation revealed that ischemic segments only existed in MINS patients. Thus, adenosine stimulation was a useful tool to finely distinguish patients with non-clinically evident cardiac lesions that are associated with poorer prognosis as observed in our MACE results. Sixth, intraoperative hypotension requiring therapy was equally frequent in MINS and controls; however, intraoperative bleeding and intra and postoperative shock were only found in MINS. Both the bleeding and shock occurring in the MINS patients are well-known causes of myocardial oxygen supply–demand mismatch. Thus, bleeding and shock, linked with a frequent although undetected CAD, are probably the ultimate causes of many of the observed MINS in our study. These results agreed with those found in the OPTIMUS and CORONARY Vision-CCTA studies which attributed two-thirds of the myocardial damage observed after non-cardiac surgery to the supply–demand imbalance mechanism, whereas only one-third could be attributed to atherothrombosis [11, 19]. And, seven, whatever the cause at their origin, the occurrence of MINS was associated with a 15%

frequency of MACE in the 1-year follow-up, whereas in the control group any MACE was detected in the follow-up. This result outlines the importance of MINS screening and diagnosis.

Implications for practice and research

Understanding the pathophysiology of MINS is crucial to develop potential prophylactic and therapeutic interventions to improve the prognosis of patients undergoing noncardiac surgery. Our results, as hypothesis generating from a pilot study, must be confirmed by further large studies, but could inform prophylactic and therapeutic interventions, and eventually, improve the prognosis of MINS patients. Moreover, our study was performed in two Spanish hospitals, so further large research involving a more racially diverse study population will help to extend the clinical implications of our results.

Limitations and strengths

We acknowledge several limitations of our study. First, we were unable to achieve initially estimated sample size. A small size, with a low number of patients in the control group, makes difficult to provide some statistically significant conclusions. As mentioned, we screened 373 individuals in each group, but the losses due to failing a complete hs-cTnT sampling, the reluctancy of the controls to undergone imaging tests, the difficulty for displacements of old, frail patients recently operated and the temporal coexistence of part of the 1-year follow-up with COVID waves that restricted the participation of individuals could explain our small recruitment. A study with a very close design as our protocol, included 46 patients with myocardial injury and 20 controls after screening 1205 candidates in pre-COVID times [23]. Therefore, our results should be interpreted as a pilot study, providing a "proof of concept" paving the way to design further studies in this field. Second, the assumptions made at the time of initial protocol development were superseded by the higher significant CAD-RADS ≥ 3 atherosclerosis frequency found by CCTA both in MINS (30.0%) and controls without MINS (33.3%) (Table 3). Third, we assessed coronary anatomy by CCTA and cardiac functionality by MRI after surgery; thus, it is possible that some of the cardiac findings existed before the intervention. Fourth, our selection criteria resulted in a population of patients with not known CAD and with or without isolated MINS; our results may be difficult to apply to other populations.

Regarding strengths, our study has some. The study addresses a very important topic in perioperative medicine, often not addressed in clinical practice, and provides some new knowledge using fine techniques as high-sensitive cardiac troponin, CCTA and cardiac MRI. In our knowledge, this is the first application of CCTA together with cardiac MRI in the evaluation of major non-cardiac surgery patients. We identified two different groups in our subjects with some similarities in coronary anatomy and occurrence of coronary disease features, but clear differences regarding cardiac ischemia and adverse outcomes in the follow-up that only were observed in patients with MINS. These observations reinforce the need of implementing systematic screening in major non-cardiac surgery patients to identify MINS and implement therapies that could decrease their occurrence.

Conclusions

This study with advanced imaging methods found a similar CAD frequency in MINS and control patients, but that cardiac ischemic findings in the MRI exploration and worse prognosis were only observed in MINS patients. Our results, obtained in a pilot study, suggest the need of further, extended studies that screened systematically MINS and evaluated its relationship with cardiac ischemia and poor outcomes.

Abbreviations

MINS	Myocardial injury after non cardiac surgery
CAD	Coronary artery disease
CAD-RADS	Coronary Artery Disease-Reporting and Data System
CCTA	Cardiac computed tomography angiography
MRI	Magnetic resonance imaging
ECG	Electrocardiogram
MACE	Major cardiovascular events
hs-cTnT	High-sensitive cardiac troponin
URL	Upper reference percentile
RCRI	Revised Cardiac Risk Index
LGE	Late gadolinium enhancement
LVEF	Left ventricular ejection fraction

Supplementary Information

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Additional file 1. STROBE-Checklist.

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Disclaimer

The funders had no role in the study design, data collection, management, analysis, writing of the report, the decision to submit the report for publication, and they will not have ultimate authority over any of these activities.

Dissemination declaration
The dissemination of data results to study participants and or patient organizations in this research project is not possible/applicable as the data are de-identified.

Patient and public involvement
Patients were not involved in the design, conduct and reporting of this study as it was not applicable to this research project.

Transparency declaration
Authors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and if relevant) have been explained.

Author contributions
JAG and EP wrote the original manuscript. JAG, EP, PAC, FCC, JOL and JZ made substantial contributions to conception and design of the study. PAC, JOL, FCC and IFG contributed to writing, review and editing. JAG, EP, MVB, MdN, GO, MRL, AHM, ESG, PPI, XGMM, DVM, RLP, IFG ensured project administration, data curation visualization. JAG, JZ and JOL performed formal analysis. EP and PAC ensured funding acquisition. PAC and FCC both senior authors contributed equally to supervision, re-view and editing of this work. All authors warrant that they have reviewed and approved the manuscript prior to submission, and they accept the responsibility for the information contained in the submission. All authors read and approved the final manuscript.

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Availability of data and materials
The data used in the present study is part of a larger dataset. The datasets generated and analysed during the current study are available and can be supplied from the corresponding authors upon reasonable request. The data not used for this manuscript will be employed in future manuscripts.

Declarations

Ethic approval and consent to participate
The study ethics approval was obtained from corresponding Ethical Committees (Hospital Universitari de la Santa Creu i Sant Pau, and Hospital Univestitari Vall d'Hebron, Barcelona, Spain) on 11/05/2016. Specific written informed consent for the image study was provided by the patients before recruitment during index hospitalization. All methods were carried out in accordance with relevant guidelines and regulations. Study was registered at Clinicaltrials.gov (NCT03438448).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Publisher's Note

5. DISCUSIÓN

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Esta tesis, como compendio de tres artículos publicados, se ha desarrollado con el fin de obtener un mayor conocimiento sobre la LMP en pacientes de alto riesgo CV sometidos a cirugía mayor no cardiaca. Esto se ha logrado mediante la implementación del cribado sistemático con TncT-as, la evaluación de la coste-efectividad de dicho cribado y el estudio de las posibles fisiopatologías asociadas a la LMP, detectables mediante técnicas avanzadas de imagen como la TCC y la RMC. A continuación, se describen y discuten los hallazgos principales de cada uno de los tres estudios.

ESTUDIO I: Implementación del cribado sistemático con TncT-as

En el estudio I, cuyo objetivo era la implementación del cribado sistemático con TncT-as en la práctica clínica, se identificaron facilitadores y barreras; información valiosa que puede ser de ayuda y servir como ejemplo práctico para otros centros que adopten esta acción a nivel nacional e internacional.

Este estudio contó con facilitadores importantes que contribuyeron al cumplimiento de los objetivos al implementar nuevos protocolos (58). En primer lugar, la fácil comprensión del protocolo por parte de los profesionales encargados de su aplicación y, sobre todo, por los pacientes participantes. Asimismo, la dedicación del equipo investigador multidisciplinario fue fundamental, ya que una parte significativa del protocolo implicaba trabajo adicional al habitual.

Sin embargo, a pesar de la facilidad de la aplicación del protocolo y los argumentos existentes respecto a su utilidad (18), el proceso de implementación del cribado con TncT-as en el Hospital de la Santa Creu i Sant Pau no estuvo exento de barreras y complejidades, como la falta de soporte de departamentos clave como Informática, atribuible a la excesiva carga de trabajo de dicho departamento. Finalmente, a pesar del esfuerzo y dedicación del equipo investigador, al finalizar el estudio, el cribado sistemático no fue adoptado por los servicios quirúrgicos participantes, excepto uno.

El estudio ha podido establecer la frecuencia de LMP en un grupo numeroso de pacientes y su relación con los factores pre-, intra y postquirúrgicos, así como con las complicaciones severas en el seguimiento a 1 mes y 1 año. La LMP fue diagnosticada en uno de cada seis (15,7%) pacientes incluidos, siendo especialmente prevalente en pacientes sometidos a intervenciones quirúrgicas urgentes y con antecedentes CV como IM o FA o de otros factores de riesgo CV como HTA, DM o de disfunción renal.

La LMP también se asoció con complicaciones intraoperatorias o postoperatorias inmediatas, como hipotensión, sangrado, anemia o alteraciones del ritmo cardíaco, muchas de las cuales pueden desequilibrar la demanda y la oferta de O_2 y provocar lesiones miocárdicas no relacionadas con la aterotrombosis.

Cabe destacar que una de las razones implicadas en este desequilibrio puede atribuirse al sangrado perioperatorio, especialmente en pacientes con LMP, quienes ya presentaban valores de Hb más bajos antes de la cirugía (p<0,001). Estos pacientes también mostraron una mayor incidencia de sangrado durante la cirugía (7,8% vs. 3,3%; p=0,004), empeorando aún más en el periodo postoperatorio inmediato (72 h) (17,3% vs. 8,1%; p<0,001). Estos resultados indican que antes de la cirugía, debería evaluarse el riesgo de sangrado quirúrgico para minimizar las pérdidas sanguíneas y confirman la importancia de corregir la anemia preoperatoria con el fin de mejorar el aporte de O_2 a los tejidos y disminuir el riesgo de transfusión. Ambos son factores modificables, por lo que no es sorprendente que esta consideración forme parte integral del protocolo ERAS como *Patient Blood Management (PBM)*, junto con otras estrategias.

Durante el período de seguimiento (un mes y un año), los pacientes con LMP presentaron mayor incidencia de CCVM (9,5% vs. 3,6% al mes y 8,6%% vs. 4,3% al año) comparando con pacientes sin LMP. Con respecto a los componentes individuales de las CCVM durante el primer mes de seguimiento, el IM fue más frecuente en los pacientes con LMP que en aquellos sin LMP (3,0% vs. 0,3%). Durante el seguimiento de un año, los pacientes con LMP presentaron más casos de ICC (6,0% vs. 2,6%), lo que refuerza la importancia de detectar sistemáticamente la LMP durante la hospitalización para evitar la aparición futura de ICC. Igualmente, esta incidencia de ICC hace recomendable la evaluación de los signos o síntomas de ICC tras el alta hospitalaria porque el control óptimo de los factores de riesgo asociados a la LMP, como la hipertensión, DM, la obesidad y el tabaquismo podría reducir su aparición en estos pacientes. No fue sorprendente que las intervenciones coronarias percutáneas como la revascularización cardiaca sólo se requirieron en pacientes con LMP (1,4%).

La incidencia de mortalidad por cualquier causa o por causa CV durante el primer mes de seguimiento fue la misma en los pacientes con o sin LMP (1,7% y 0,9%, respectivamente). Sin embargo, durante el seguimiento hasta un año tanto las muertes por cualquier causa como aquellas de causa CV (11,2% y 3,9%, respectivamente) se elevaron fuertemente en los pacientes con LMP frente a un aumento más ligero en los pacientes sin LMP (6,3% y 1,8%). Estos datos subrayan la gravedad pronóstica de esta condición y la importancia del cribado sistemático y su detección precoz.

Por último, y aunque no fue objetivo específico del programa de cribado debe comentarse que la infección fue la complicación más frecuente en los casos con LMP que en aquellos sin LMP (23,3% vs. 14,5%) durante el primer mes del postoperatorio. Las tasas de infección disminuyeron al cabo de un año, pero continuaron siendo elevadas (LMP: 10,5% vs. no LMP: 7,1%). Este hecho sugiere que un programa ideal de cribado como el del estudio no solo debería incluir variables y marcadores CV, sino también marcadores de infección adicionales, más sensibles y específicos que, por ejemplo, los contajes

leucocitarios que pueden alterarse simplemente por el estrés quirúrgico; la procalcitonina podría ser uno de estos biomarcadores.

El conjunto de estos datos indica que los pacientes con enfermedades o factores de riesgo CV constituyen un grupo en el cual debe aplicarse el cribado sistemático con TncT-as para identificar a aquellos con LMP. Un control riguroso preoperatorio de factores de riesgo CV y el tratamiento óptimo de aquellas condiciones intra o postoperatorias más asociadas con la LMP puede prevenir o, al menos, disminuir las complicaciones. Se puede concluir que los datos observados en pacientes con LMP respaldan la implementación del cribado sistemático de la condición; sin olvidar que las tasas de CCVM o la mortalidad en los pacientes que no presentan LMP no son, en absoluto, negligibles.

ESTUDIO II: Coste-efectividad del cribado sistemático con TncT-as

El estudio II cuyo objetivo fue evaluar el coste-efectividad del proceso de cribado sistemático de la LMP con de TncT-as, comparado con la práctica clínica habitual ha aportado la información valiosa para nuestro sistema sanitario. La estrategia del cribado permitió detectar 10 veces más casos de LMP (15,7% vs. 1,6%), que la estrategia de práctica clínica habitual. Esta elevada tasa de LMP y la superioridad de la estrategia del cribado sistemático pueden atribuirse al uso de un biomarcador cardiaco más sensible y específico que los síntomas de la isquemia cardiaca, los cuales muchas veces están enmascarados en el periodo postoperatorio por la sedación y analgesia, y no se detectan sin el cribado. Es importante tener en cuenta que la cohorte estudiada incluyó a pacientes de edad avanzada, casi un 95% mayores de 65 años, lo que debe considerarse para un diagnóstico preciso de LMP (59,60). Además, los pacientes incluidos presentaban frecuentemente factores de riesgo CV clásicos como HTA, DM, dislipemia, FA o deterioro de la función renal. Todos estos factores de riesgo CV están asociados con concentraciones de TncT-as superiores al límite superior de referencia obtenido en población general sana y de menor edad media (61).

Adicionalmente, el estudio II ha proporcionado por primera vez, una estimación de la relación de coste-efectividad incremental (ICER) asociado a la detección de LMP que fue de 425 €/caso detectado y ha demostrado que el cribado sistemático con TncT-as en pacientes de alto riesgo CV puede ser eficiente a corto plazo con una disposición a pagar más que razonable.

ESTUDIO III: LMP evaluada con imagen cardiaca avanzada

.El estudio III, un estudio piloto que incluyó 52 pacientes con LMP y 12 controles sin LMP, ha evaluado las potenciales fisiopatologías asociadas a la LMP que son detectables mediante técnicas avanzadas de imagen como TCC y RMC. Los pacientes incluidos en este estudio eran representativos de los pacientes con LMP del estudio I ya que presentaban similares factores de riesgo CV. Sin embargo, en este estudio

piloto los pacientes con LMP recibieron más cirugía electiva (82,7%) que la población total del estudio I (58,9%). La principal diferencia con los pacientes con LMP del estudio I fue la mayor incidencia de sangrado intraoperatorio (10,4% vs. 7,8%) y mayor frecuencia de shock tanto intraoperatorio (16% vs. 8,2%) como postoperatorio (10% vs. 6,3%). Las concentraciones de TncT-as postoperatorias de los pacientes con LMP aumentaron 4 veces a las 48 horas del postoperatorio (41 ng/L vs. 11 ng/L) y 3 veces a las 72h (31 ng/L vs. 11 ng/L) frente a las observadas en los pacientes control, sin LMP.

En las pruebas de imagen cardíaca avanzadas, TCC y RMC, se observó una incidencia de EAC similar en los pacientes con LMP y los pacientes control. Sin embargo, en la RMN de los 13 pacientes con LMP y seis pacientes control con índice CAD-RADS≥3 y sometidos a la prueba de adenosina se observaron anormalidades de la perfusión de la pared cardíaca o segmentos isquémicos en siete de los casos con LMP y sólo en un sujeto control.

Los resultados del estudio III sugieren que la LMP de los pacientes analizados puede ser el resultado del desequilibrio en la demanda y la oferta de O_2 en miocardio causado por factores no aterotrombótica como el sangrado, la hipotensión y/o el shock, todos los factores ligados al incremento de Tnc (62). Este patrón fisiopatológico no es inocuo ya que, en el seguimiento a un año, un 15,4% de los pacientes con LMP del estudio sufrieron una CCVM frente al 0% en los sujetos control, así como una mortalidad por cualquier causa elevada (7,7%) que se registró únicamente en los pacientes con LMP.

5.1. Discusión de los resultados en el contexto del conocimiento actual

5.1.1. ESTUDIO I: Implementación del cribado sistemático con TncT-as

En la última década, las recomendaciones sobre la importancia del cribado de la LMP, especialmente en pacientes con mayor riesgo CV y vital, se han recogido en muchas guías de sociedades científicas internacionales (18-19, 26-33). El diseño del estudio I está en concordancia con las recomendaciones de la guía más reciente de la ESC del año 2022 (18), e incluso con las más cautelosas recomendaciones de ESAIC 2023 (63). A pesar de haberse diseñado e iniciado seis/siete años antes (a partir de 2016) de que dichas guías fueran publicadas, su diseño se ajusta literalmente a las recomendaciones actuales. Este hecho se atribuye a la experiencia previa del equipo investigador, que participó activamente en estudios significativos que generaron evidencia científica sobre el uso de biomarcadores cardíacos en general (64,65) y, específicamente, en cirugía no cardiaca (9,16), durante los años 2012 y 2015.

Sin embargo, la implementación del cribado sistemático con Tnc en la práctica clínica y la evidencia derivada de su aplicación en experiencias locales son aún muy limitadas, ya que sigue siendo un tema controvertido (63,66-68). Esta situación puede atribuirse a causas como la ausencia de un consenso universalmente aceptado, sobre la definición y los criterios diagnósticos de la LMP - como el que existe para el infarto de miocardio (IM), la falta de datos suficientes sobre las estrategias para su tratamiento o la incertidumbre acerca del impacto que el cribado sistemático pueda tener en los resultados centrados en los pacientes (69,70). Una de las causas más importantes que podría justificar esta falta de adopción del cribado es que, una vez detectada la existencia de LMP, la etiología plural de la misma dificulta adoptar una intervención terapéutica específica adicional a mantener el mejor estado postoperatorio posible del paciente y tratar las complicaciones que presente (69). Por este motivo, se han desarrollado diversos ensayos clínicos para evaluar estrategias terapéuticas que disminuyan el riesgo de CCVM en los pacientes intervenidos de cirugías no cardíacas.

Hasta la fecha, existe un único ensayo clínico multicéntrico y multinacional, denominado MANAGE (71) sobre la utilidad de un tratamiento específico de la LMP para prevenir las CCVM. Este ensayo incluyó 1754 pacientes que recibieron un amplio espectro de cirugías no cardiacas; a los pacientes con LMP se les administraron 110 mg de dabigatrán - un inhibidor de la trombina- dos veces al día o placebo hasta finalización del estudio o por un máximo de dos años. El estudio concluyó que el dabigatrán reducía el riesgo del resultado compuesto, que incluía muerte por causa vascular, IM, AVC no hemorrágico, trombosis arterial periférica, amputación y tromboembolismo venoso sintomático, sin que existiera un aumento significativo de sangrado grave. Sin embargo, la incidencia de IM o la necesidad de revascularización coronaria fueron similares en el grupo tratado y en el grupo placebo. Una limitación significativa del ensayo clínico fue que el dabigatrán se interrumpió en casi la mitad de los pacientes

(46%) y una proporción similar (43%) abandonó el placebo. Esta limitación dificulta la evaluación del riesgo de sangrado a largo plazo y plantea dudas sobre su aplicabilidad clínica.

Aunque la LMP no fue el objetivo fundamental, los resultados del estudio POISE en el año 2008, uno de los primeros sobre cirugía no cardíaca y sus complicaciones y que incluyó a 8351 pacientes, demostraron que el tratamiento perioperatorio con un betabloqueante (Metoprolol) frente a placebo reducía la incidencia de muerte de causa vascular (5,8% vs. 6,9%), IM (4,2% vs. 5,7%) y paro cardíaco no fatal (11). Sin embargo, en los pacientes con metoprolol se observó un aumento en la mortalidad global (3,1% vs 2,3%), AVC (1,0% vs 0,5%), hipotensión clínicamente importante y bradicardia frente al placebo. Los beneficios quedaban parcialmente contrarrestados por los riesgos.

Posteriormente, el estudio POISE-2, del mismo grupo de investigadores, observó e en 10 010 pacientes que la administración perioperatoria de aspirina y clonidina frente a placebo no disminuía la incidencia de muerte o IM, pero sí aumentaba la incidencia de sangrado grave, hipotensión y bradicardia (72,73). Finalmente, en el estudio POISE-3, mostró en 9535 pacientes que el ácido tranexámico administrado antes y después de la cirugía no cardiaca redujo la incidencia de sangrado mayor (9,1%) frente a placebo (11,7 %). Además, la incidencia del resultado compuesto con una combinación de sangrado potencialmente mortal, sangrado grave y sangrado en un órgano crítico fue significativamente más bajo con ácido tranexámico que con placebo. Sin embargo, no se pudo establecer la no inferioridad del ácido tranexámico frente a placebo con respecto al resultado CV compuesto que incluía LMP, AVC no hemorrágico, trombosis arterial periférica y tromboembolismo venoso proximal sintomático (74).

Otro estudio multicéntrico y multinacional que incluyó 3209 pacientes de edad ≥55 años, intervenidos exclusivamente de cirugías torácicas, comparó la colchicina oral (0,5 mg, dos veces/día) con un placebo equivalente. El tratamiento se administraba cuatro horas antes de la cirugía y continuaba durante diez días. El no solo evaluó la LMP, sino también la aparición de nueva FA clínicamente importante. El seguimiento se desarrolló durante 14 días tras la cirugía. El estudio concluyó que la administración de colchicina no reducía ni la incidencia de la LMP ni de la FA clínicamente importante. No obstante, al analizar conjuntamente la incidencia de la LMP y la FA como un resultado compuesto, la colchicina mostró ser efectiva comparada con el placebo en reducir su incidencia, aunque también aumentó el riesgo de diarrea no infecciosa (75).

La cohorte del estudio I, incluyó principalmente a pacientes de edad avanzada (94.8% ≥65 años) con un elevado riesgo CV, y no es de extrañar que muchos de ellos estuvieran ya en tratamiento con fármacos cardiovascularmente activos antes de la cirugía. En el periodo preoperatorio, el uso de IECAs, aspirina, betabloqueantes y anticoagulantes orales (ordenados por frecuencia de uso) fue significativamente más frecuente en los pacientes con LMP (p=0,003 a 0,009 vs. no LMP). Esta proporción diferencial en el uso

de medicación CV se mantuvo a lo largo de todo el periodo de seguimiento (p entre 0,032 y <0,001 para los diferentes tratamientos). En contraste, las estatinas se utilizaron de manera generalizada y similar en los pacientes con y sin LMP. En el momento de la realización del estudio, los investigadores del grupo se basaron en las guías de la ESC/EAS de 2014 (27), que recomendaban considerar el uso de aspirina y estatinas según los factores de riesgo CV de los pacientes. Dado que los factores asociados con la aparición de LMP podían ser de causa no aterotrombótica, no se consideró apropiado aumentar el uso de aspirina o medicamentos anticoagulantes/antiagregantes plaquetarios tras el diagnóstico de LMP. Por lo tanto, el diagnóstico de LMP no condujo a cambios significativos en el uso de medicamentos. No se consideró el uso de dabigatrán, ya que el estudio MANAGE (71) se publicó dos años después del inicio del estudio I.

En cuanto al diseño del programa de cribado, en el estudio se protocolizaron mediciones seriadas de TncT-as antes de la cirugía y a las 48-72 h de la misma, con el objetivo de distinguir los cambios agudos atribuidos a la LMP de las elevaciones crónicas causadas por otras razones; este fue un hecho diferencial frente a otros estudios iniciales que analizaron las concentraciones de Tnc exclusivamente tras la cirugía (9,16). Es de reseñar que se ha descrito que la mayoría de las LMP ocurren en las primeras 48 h postcirugía; sin embargo, muchos estudios en los que se basa esta observación carecen de la determinación de Tnc previa a la cirugía. La falta de la determinación de Tnc basal (preoperatoria) resta especificidad diagnóstica a la evaluación de los valores postquirúrgicos como indicadores de una lesión miocárdica aguda. La medición seriada pre y postoperatoria de Tnc-as no fue recomendada hasta el año 2018 por las guías de la Sociedad Europea de Anestesiología (30) y respaldada por un consenso de expertos en el año 2021(14).

Al analizar los estudios iniciales publicados sobre el papel de Tnc en el diagnóstico de la LMP, es importante considerar que los estudios previos, a diferencia de estudio I, utilizaron métodos contemporáneos para medir el biomarcador con menor sensibilidad analítica y, consecuentemente, menor sensibilidad diagnóstica para LMP poco extensas. Métodos de alta sensibilidad han reemplazado progresivamente a los métodos contemporáneos (21,22). Un ejemplo del efecto de esta transición de métodos re refleja en el estudio VISION (15). Dado que el reclutamiento de este estudio abarcó un periodo de cinco años, se utilizó Tnc contemporánea para los primeros 15 000 pacientes y TncT-as para los más de 21 000 pacientes reclutados posteriormente. Otro detalle para considerar es que los métodos de alta sensibilidad están disponibles tanto para TncT como para TncI, y varios estudios midieron TncI-as y no TncT-as (76). Todas estas diferencias y discrepancias deben considerarse al interpretar y comparar los resultados del estudio I con otros estudios, ya que las comparaciones podrían no ser exactas ni precisas.

Como ya se ha mencionado en la introducción, actualmente la LMP se denomina con dos términos diferentes: MINS (16) o PMI (13). En el estudio I, se usó el término LMP y se definió como una elevación de la concentración de TncT-as del 50% con respecto al valor preoperatorio, por encima del percentil 99 superior de referencia. Este criterio se estableció teniendo en cuenta la información disponible en el momento del diseño del estudio (52-53, 77-78) y basándose en la experiencia previa del equipo investigador (9, 16). No obstante, a pesar del uso de diferentes términos y criterios para definir la LMP, así como las posibles diferencias en las poblaciones estudiadas, la elevada incidencia de LMP observada en el estudio I coincide con los resultados de otros estudios (9, 13, 16), especialmente con el estudio BASEL-PMI (13), que utilizó el mismo diseño que el estudio I y midió TncT-as antes y después de la cirugía, observando una incidencia de LMP del 16%, muy similar a la cohorte del estudio I que fue del 15.7%.

La discrepancia en la denominación de un mismo hecho fisiopatológico resalta la necesidad de unificar y estandarizar la terminología utilizada para describirlo, con el fin de facilitar la comunicación y la comprensión de esta patología entre la comunidad médica que atiende a los pacientes con riesgo de LMP. Una definición estandarizada y una clasificación precisa ayudarían a aumentar la concienciación sobre la importancia de la LMP y a mejorar su detección precoz y prevenir sus complicaciones.

5.1.2. ESTUDIO II: Coste-efectividad del cribado sistemático con TncT-as

Hasta la fecha, la investigación científica descrita en el apartado **1.4.2.**, a pesar de las notables diferencias existentes en el tipo de poblaciones estudiadas, horizontes temporales de los estudios y tipos de análisis económicos empleados respecto al presente estudio II, ha demostrado que el cribado sistemático con Tnc en pacientes sometidos a cirugía no cardiaca puede ser coste-efectivo. También es relevante destacar que los tres estudios previos (39-41) midieron Tnc con métodos contemporáneos, a diferencia del estudio II que utilizó un método de alta sensibilidad. Además, en los tres estudios previos, la Tnc se midió exclusivamente después de la cirugía, a diferencia del modelo del estudio II que midió TncT-as pre y post operatoriamente.

El estudio más precoz sobre el coste-efectividad de la detección de LMP se publicó en el año 2007 (39). Este estudió se basó en los resultados publicados hasta el año 2006 sobre el uso de TncI en cirugía abdominal abierta de aneurisma aórtico para mejorar el estado de los pacientes, mientras estuvieran ingresados en las UCI, y su evolución posterior. Los autores completaron un modelo de Markov, basándose en datos disponibles en la literatura, y asumieron una probabilidad de LMP del 4,9% así como la eficacia de las intervenciones tempranas en la UCI para reducir el IM en pacientes con TncI elevada en el periodo perioperatorio de 0.55. El horizonte temporal fue más extenso (toda la vida) en contraste con el estudio II, que se elaboró sólo a corto plazo (30 días). El beneficio para la salud se midió en QALYs

– medida diferente a la aplicada en el estudio II - y el ICER se calculó como la ratio coste/QALY y fue de $12,641 dólares (año 2006). A pesar de las significativas diferencias metodológicas, la conclusión de este estudio y del estudio II fue que el ICER era coste-efectivo y justificaba el cribado con Tnc, tanto en los pacientes de cirugía vascular como en el estudio II desarrollado en todo tipo de cirugías no cardíacas.

En el año 2014, Torborg y colaboradores desarrollaron un análisis fármaco-económico de costo-efectividad, en el que a los pacientes intervenidos de cirugías no cardíacas y con TncT elevada se administró un tratamiento con aspirina y estatinas para prevenir infarto de miocardio (IM) o la muerte (40). Los autores de este estudio asumieron un riesgo relativo del 25% para la mortalidad vascular y el IM tras el inicio del tratamiento con aspirina y estatinas en los pacientes con TncT elevada. Hay que tener en cuenta que, en este estudio, todos los costes utilizados fueron promedios basados en los costes de la sanidad privada de Sudáfrica (en el año 2014), a diferencia de los otros dos estudios iniciales (39 y 41), así como del estudio II que se realizaron en el ámbito de la sanidad pública. Los costes medios de los fármacos utilizados en pacientes con TncT elevada fueron aspirina a dosis bajas (80-100 mg/día) y estatinas (atorvastatina genérica, 40 mg/día) durante 30 días. Para los ingresos hospitalarios se utilizó el sistema de Grupos Relacionados por el Diagnóstico (GRD). El cribado sistemático con Tnc para el inicio del tratamiento con aspirina y estatina resultó costo-efectivo, con un coste incremental de aproximadamente $898 (al cambio actual del Rand sudafricano) por evento evitado.

Finalmente, el tercer estudio se publicó en el año 2018 por los investigadores canadienses que desarrollaron un análisis de coste-consecuencia que incluyó a 6021 pacientes del estudio VISION (41). La tasa de mortalidad a los 30 días asociada a la LPM fue del 9,6% muy superior a la detectada en el estudio II (1,7%). Una explicación plausible y posible es que en el estudio VISION la LMP se diagnosticó con TncT medida con métodos contemporáneos que requería observar una concentración de TncT ≥30 ng/L, mientras que midiendo TncT-as la LMP se diagnostica con concentraciones dos veces inferiores ≥14 ng/L. En el estudio VISION, obviamente, se incluyeron como LMP los pacientes con isquemias miocárdicas más extensas, asociadas con mayor morbimortalidad, comparando con el estudio II donde la TncT-as ha detectado los casos de LMP mucho menos extensas. El coste adicional de la detección de una LMP con TncT fue de $1632 (dólares canadienses del año 2015); este coste, lógicamente, fue menor en los pacientes con alto riesgo y en los mayores de 65 años o en aquellos con antecedentes de aterosclerosis o DM (coste adicional de $1309). En consecuencia, los resultados demostraron que los costes del cribado con TncT para detectar LMP fueron moderados y que el coste-consecuencia en términos de ganancia de salud sugiere que la implementación de este cribado puede ser especialmente coste efectivo en los casos con alto riesgo de LMP tras la cirugía.

Para concluir, las comparaciones entre los resultados del estudio II y de los estudios previos deben interpretarse con cautela por la multiplicidad de factores diferenciales: como diferencias en los análisis económicos realizados, en las estructuras de los sistemas de salud y, especialmente, en el quien da soporte económico - público o privado- a la atención de salud. En concreto, el estudio II se basó en los costes del personal sanitario, medicamentos, laboratorio, estancias hospitalarias, etc., del sistema nacional de salud de Catalunya; por lo tanto, estos costes podrían diferir, siendo posiblemente inferiores a los de otros estudios que involucren costes distintos a los utilizados en el estudio II.

5.1.3. ESTUDIO III: LMP evaluada con imagen cardiaca avanzada

Las pruebas de imagen cardíaca avanzada, como la TCC y la RMC, son muy útiles para evaluar la fisiopatología de LMP, pero su uso está limitado por sus elevados costes, la disponibilidad de la instrumentación y de profesionales expertos en su manejo e interpretación en nuestro sistema de salud, especialmente para fines de investigación.

Los resultados observados en el estudio III coincidieron con dos estudios previos, OPTIMUS (47) y VISION-CTA (48), al observar que en los pacientes sometidos a cirugía no cardiaca la aterotrombosis solo estaba implicada en aproximadamente un tercio de los casos de LMP. Es relevante señalar que, a diferencia del estudio III, las pruebas de imagen cardíaca en ambos estudios previos se realizaron exclusivamente antes de la cirugía y no después de la misma como en el estudio III. En el estudio OPTIMUS, la TCC preoperatoria mejoró el valor predictivo del riesgo de daño miocárdico postoperatorio. No obstante, en el estudio VISION-CTA, muchos pacientes con lesiones coronarias graves en la TCC preoperatoria no presentaron complicaciones postoperatorias, lo que sugería que la TCC preoperatoria podría sobrestimar el riesgo postoperatorio en estos pacientes. En este mismo estudio, los autores concluyeron que la RMC podría mejorar la identificación de los pacientes con riesgo de complicaciones postoperatorias.

En el estudio III, se observó que tanto el sangrado significativo (7,8% en el perioperatorio, 17,3% en el postoperatorio), el shock (8,2% en el perioperatorio, 6,3% en el postoperatorio) y la EAC previa (17,7% antecedentes de IM) fueron significativamente más frecuentes en los pacientes con LMP que en aquellos sin LMP que presentaron, aproximadamente, la mitad de las complicaciones referidas. Estos resultados sugieren, como los de los estudios OPTIMUS y VISION-CTA, que la mayor parte de los casos de LMP observada pueden atribuirse a mecanismos de desequilibrio oferta-demanda de O_2 al miocardio no atribuibles exclusivamente a la aterotrombosis (79,80). Es importante tener en cuenta que en el estudio III, tanto la prueba de TCC como la RMN se realizaron solo después de la cirugía. Lógicamente, las lesiones anatómicas coronarias observadas por TCC, no podían considerarse como consecuencias,

sino como causas de las alteraciones funcionales observadas mediante RMC; por lo tanto, estos resultados solo serían aplicables a estudios con un diseño similar.

En un estudio realizado en Holanda (42), muy similar al estudio III por el tamaño muestral, la edad y estado de salud de los pacientes, se utilizaron ambas pruebas (TCC y RMC) después de la cirugía no cardíaca. La RMC se realizaba únicamente en los pacientes que presentaban EAC significativa en la TCC, que fueron la mayoría (85%). Además, en este estudio se midió TncI con un método contemporáneo. Estas diferencias respecto al estudio III podrían causar variaciones en la asignación diagnóstica de los pacientes. El estudio observó realce tardío de gadolinio y defecto de perfusión en aproximadamente un tercio de los casos con LMP (31.8%), resultados muy similares (28.2% de los casos) a los encontrados en el estudio III. Sin embargo, este estudio objetivó la existencia de EP clínicamente silente en un tercio de los pacientes con LMP, mientras que en el estudio III no se observó ninguna EP ni en los pacientes con LMP ni en los controles. Diferencias en el diseño y los limitados tamaños muestrales podrían estar en el origen de las diferencias entre ambos estudios.

Cabe mencionar la dificultad para reclutar pacientes con LMP o sin ella para la realización de pruebas de imagen complejas, la cual se evidenció durante el desarrollo del estudio III. El estudio holandés (42), antes mencionado, con un diseño muy semejante, ha tenido la misma (incluso mayor) dificultad para alcanzar el tamaño de la muestra inicialmente estimado. Incluyó únicamente a 46 pacientes con LMP de 1205 elegibles y 20 controles, datos inferiores al estudio III, donde se incluyeron 52 casos de 373 elegibles y 12 controles. En el estudio III los investigadores identificaron a 373 pacientes elegibles para cada grupo (LMP, no LMP); sin embargo, diversas dificultades como la ausencia de todas las mediciones de TncT-as por altas hospitalarias tempranas antes de 48-72 h del postoperatorio, problemas logísticos para realizar pruebas de imagen - especialmente en pacientes ancianos y frágiles recién operados y no residentes en Barcelona, así como las primeras olas de la pandemia de COVID, impidieron la participación de más pacientes en el estudio. Es relevante destacar que, en el caso del grupo de control, la negativa a participar fue aún más pronunciada que en el grupo de pacientes con LMP. Estos pacientes aparentemente sanos, sin justificación clínica para la realización de pruebas adicionales, rechazaron mayoritariamente someterse a las pruebas de imagen cardíaca avanzada solo con fines de investigación.

5.2. Fortalezas y limitaciones de la Tesis

Los tres estudios de la presente tesis tienen en común: 1) que son los primeros realizados en España en sus respectivos ámbitos de investigación, 2) que se han realizado en pacientes con elevado riesgo de CV, 3) que el biomarcador empleado para el cribado sistemático de LMP - la medida de TncT-as - es el más adecuado para detectar concentraciones muy bajas del biomarcador, lo que contribuye a una tasa de detección de LMP más elevada en comparación con numerosos estudios previos, 4) que la especificidad diagnóstica de la LMP se ha maximizado al medir TncT-as pre y post operatoriamente y, finalmente, 5) que el diseño del estudio se ajusta a las recomendaciones de las guías de la ESC del año 2022 (18) a pesar de haberse sido diseñado y desarrollado 6 años antes su publicación.

Las principales fortalezas y limitaciones específicas de cada uno de los estudios se resumen en la **Tabla 1** y la **Tabla 2**.

Tabla 1. Fortalezas de los estudios incluidos en la tesis.

Estudio	Fortalezas
ESTUDIO I: Implementación del cribado sistemático con TncT-as	- El estudio ha sido desarrollado por un equipo de investigación multidisciplinario, constituido ad hoc, con amplia experiencia previa en la línea de investigación del estudio. - El diseño del protocolo fue pragmático y fácilmente aplicable para los profesionales de la salud, así como comprensible para los pacientes. - Se ha determinado la prevalencia de LMP y su asociación con CCVM y mortalidad a los 30 días y al año después de la cirugía no cardiaca en una amplia cohorte de un hospital terciario de España. - Se ha llevado a cabo un seguimiento completo tanto a corto plazo (30 días) como a largo plazo (un año).
ESTUDIO II: Coste-efectividad del cribado sistemático con TncT-as	- El diseño del estudio ha sido desarrollado por un equipo de investigación multidisciplinario, incluyendo investigadores clínicos y economistas de la salud. - Ha sido el primer estudio realizado en España que ha analizado la evaluación económica de la detección de LMP. - Se ha estimado la ratio de coste-efectividad incremental (ICER) para cada nuevo caso de LMP detectado. - Se ha estimado una disposición a pagar (WPT) para cada caso de LMP detectado. - El cribado sistemático ha permitido detectar diez veces más casos de LMP comparando con la práctica clínica habitual.
ESTUDIO III: LMP evaluada con imagen cardiaca avanzada	- Se ha empleado el uso combinado de las pruebas avanzadas de imagen cardiaca como la TCC y la RMC. - Se han Identificado las posibles causas no aterotrombóticas como principales responsables de la isquemia cardíaca en paciente con LMP.

Tabla 2. Limitaciones de los estudios incluidos en la tesis.

Estudio	Limitaciones
ESTUDIO I: Implementación del cribado sistemático con TncT-as	- No se incluyeron todos los pacientes elegibles por indisponibilidad del equipo investigador en algunos días festivos. - El equipo investigador fue limitado y no incluyó a todos los facultativos de todos los servicios implicados. - No se pudo conseguir la informatización de las solicitudes de TncT-as y consultas cardiológicas, que se realizaron de forma manual. - Se perdieron 10,5% de las mediciones de TncT-as en el postoperatorio debido a altas hospitalarias precoces (antes de 72 h). - El protocolo fue ejecutado exclusivamente por el equipo investigador y tras su finalización, aún no ha sido adoptado en la práctica clínica local, salvo en un servicio quirúrgico.
ESTUDIO II: Coste-efectividad del cribado sistemático con TncT-as	- El estudio, no disponía de una cohorte de comparación de la atención clínica habitual, por lo cual fue necesario utilizar una cohorte hipotética para representar la estrategia de atención habitual. - El análisis del estudio se llevó a cabo solo en el horizonte temporal a corto plazo, con un seguimiento de 30 días. - Se ha utilizado solo una estimación de la predisposición a pagar (WTP) por cada caso de LMP detectado, dado que se carecía del valor establecido previamente. - El diseño del estudio no contempló la evaluación de los resultados sobre la salud a lo largo de los años de vida ajustados por calidad (QALY).
ESTUDIO III: LMP evaluada con imagen cardiaca avanzada	- No se consiguió alcanzar el tamaño de la muestra inicialmente estimado. - En el caso del grupo de control, la negativa a participar fue más pronunciada que en el grupo de pacientes con LMP. - Las pruebas de imagen (TCC y RMC) se aplicaron únicamente en el postoperatorio.

5.3. Implicaciones

5.3.1. Para la práctica clínica

Los resultados de la presente tesis son generadores de hipótesis y nuevos conocimientos sobre LMP, potencialmente aplicables a la práctica clínica.

- La experiencia local en la implementación del cribado sistemático con TncT-as del estudio I, puede servir como un ejemplo práctico y ser adoptado por más hospitales nacionales e internacionales, contribuyendo a la concienciación y sensibilización sobre su utilidad tanto entre los profesionales de la salud como entre los pacientes que padecen esta complicación. Además, los desafíos y complejidades identificados durante el proceso de implementación reflejan la realidad de la práctica clínica habitual en la sanidad pública. Factores como la aceptación y comprensión, junto con la disponibilidad de recursos y la infraestructura necesaria, son esenciales para el éxito en la implementación de nuevos protocolos en la práctica clínica.
- Los resultados del estudio II pueden ser de utilidad para los comités de elaboración de guías de práctica clínica, especialmente en países con sistemas de salud similares al de España. El cribado sistemático con TncT-as aunque implique costes superiores a la de atención habitual, es viable y resulta coste-efectivo ya que puede contribuir a prevenir y reducir futuras complicaciones o reingresos, y en consecuencia disminuir gastos innecesarios. Cabe mencionar, que los datos del estudio II se han utilizado en dos recientes comentarios editoriales en la revista Eur J Anesthesiol (diciembre 2023) sobre el coste efectividad del cribado sistemático de LMP, subrayando la relevancia clínica de la investigación desarrollada (81,82).
- Finalmente, el uso de pruebas de imagen cardíaca avanzada, como la TCC y la RMC, así como su disponibilidad en el ámbito perioperatorio, pueden abrir nuevas perspectivas para el desarrollo de posibles intervenciones profilácticas y, sobre todo, tratamientos específicos con el objetivo de mejorar el pronóstico de pacientes con LMP.

5.3.2. Para la investigación

Los resultados de la presente tesis, que forman parte del desarrollo de la línea de investigación de medicina perioperatoria, son solo una parte y deben ser continuados por los estudios más extensos que incluyan a una población más amplia, con mayor diversidad en etnicidad y edad.

- Los tomadores de decisiones, como los investigadores involucrados en el desarrollo de nuevos protocolos de cribado sistemático con biomarcadores cardiacos (medidas con los métodos de alta sensibilidad), deberían definir con claridad los criterios de elegibilidad de los pacientes que

más podrían beneficiarse de dicho cribado y evaluar minuciosamente todos los aspectos, a favor y en contra de su implementación.

- El coste incremental del cribado sistemático con TncT-as para detectar un LMP adicional está dentro de los intervalos aceptados para su aplicación por parte de la sanidad pública, sin embargo, se deberían llevar a cabo más estudios que respalden su utilización a largo plazo, con el fin de generar evidencia más sólida.
- Finalmente, la utilidad de las pruebas de imagen cardíaca avanzada, como la TCC y la RMC en el contexto perioperatorio, deben ser confirmadas por estudios más extensos que incluyan a una población más amplia. No obstante, a pesar de tratarse de un estudio piloto, el estudio III se ha incluido en un metanálisis que está actualmente en curso y que se realiza en colaboración con un equipo holandés (Dra. Judith Van Waes, University Medical Center Utrecht, NL).

A nivel general, todos los estudios de la línea de medicina perioperatoria desarrollados en el Hospital de la Santa Creu i Sant Pau, que inició su actividad en el año 2006 mediante la participación en el ensayo clínico POISE coordinado por el *PHRI-Population Health Research Institute* (Instituto de investigación vinculado a la Universidad de McMaster, Hamilton-Ontario, Canadá), tanto a nivel nacional (incluyendo los tres estudios que forman parte de la presente tesis) como internacional, han contado con el apoyo y la colaboración de expertos en esta línea de investigación, referentes a nivel mundial.

Desde entonces, y de manera ininterrumpida, la doctoranda ha seguido colaborando de forma muy relevante en múltiples (n=12) estudios clínicos del PHRI (cuatro de ellos actualmente en curso), ampliándose progresivamente la colaboración con otros grupos internacionales relevantes como *ESAIC-European Society of Anaesthesiology and Intensive Care* y también mediante el impulso de estudios propios realizados con fondos competitivos (principalmente del Instituto de Salud Carlos III – Ministerio de Sanidad de España).

Las 18 publicaciones complementarias presentadas por la doctoranda, adjuntas al trabajo de esta tesis (**Anexo 1**), reflejan la diversidad de temas abordados, que incluyen el cribado con biomarcadores cardiacos, diversas intervenciones farmacológicas y no farmacológicas para la prevención o tratamiento de CCVM perioperatorios. Además, se han utilizado varios diseños de investigación, como ensayos clínicos controlados y aleatorizados de grupos paralelos o con diseño factorial, cohortes prospectivas o retrospectivas, así como estudios de casos y controles anidados. Todos estos estudios han sido publicados en revistas científicas con revisión por pares, algunas de alto impacto.

6. CONCLUSIONES

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- La implementación del cribado sistemático con TncT-as es factible y permite detectar la LMP en una elevada proporción de pacientes con alto riesgo CV.
- Existen barreras y complejidades para lograr la óptima y efectiva implementación del cribado sistemático en la práctica clínica habitual.
- Los pacientes con LMP presentan peores resultados durante el seguimiento a corto (30 días) y sobre todo a largo (un año) plazo.
- La estrategia de cribado sistemático con TncT-as es coste-efectiva, en un horizonte temporal de 30 días.
- La ratio coste-efectividad incremental (ICER) de 425 euros por cada LMP detectada adicionalmente, implica una disposición a pagar razonable.
- Las pruebas de imagen avanzada como la CCT y la RMC han sido de utilidad para identificar las posibles causas etiológicas de la LMP en los pacientes del estudio, revelando que la isquemia cardíaca puede ser causada por mecanismos no aterotrombóticos.

7. BIBLIOGRAFÍA

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8. ANEXOS

8. ANEXOS

Anexo 1. Publicaciones complementarias

El presente anexo describe la actividad científica - aparte de la presentada en la presente tesis que la doctoranda Ekaterina Popova Sherozia ha desarrollado en el ámbito nacional e internacional en el programa "Metodología de la Investigación Biomédica y Salud Pública" del Departamento de Pediatría, Obstetricia y Ginecología, y Medicina Preventiva y Salud Pública, Universidad Autónoma de Barcelona.

- **Publicaciones como miembro del comité director (*steering committee*) en estudios internacionales**

En guías y recomendaciones internacionales de la ESAIC (*European Society of Anesthesia & Intensive Care*)

1. Lurati Buse G, Bollen-Pinto, Abelha F, Abbott TEF, Ackland G, Afshari A, De Hert S, Fellahi JL, Giossi L, Kavsak P, Longrois D, M'Pembele R, Nucaro A, **Popova E**, et al. ESAIC focused guideline for the use of cardiac biomarkers in perioperative risk evaluation. **Eur J Anaesthesiol. 2023 Jun 2.** doi: 10.1097/EJA.0000000000001865. PMID: 37265332. Member of steering committee. IF: 4.1; (Q1).

2. Puelacher C, Bollen Pinto B, Mills NL, Duceppe E, **Popova E**, et al. Expert consensus on peri-operative myocardial injury screening in noncardiac surgery: A literature review. **Eur J Anaesthesiol. 2021 Jun 1**;38(6):600-608. doi: 10.1097/EJA.0000000000001486. PMID: 33653981. Member of steering committee. IF: 4.1; (Q1).

- **Publicaciones como miembro del comité director (*steering committee*), líder y coordinador nacional (*National Leader and Coordinator)* - en estudios clínicos internacionales**

3. Conen D, Ke Wang M, **Popova E**, et al for the COP-AF Investigators. Effect of colchicine on perioperative atrial fibrillation and myocardial injury after non-cardiac surgery in patients undergoing major thoracic surgery (COP-AF): an international randomized trial. **Lancet. 2023 Aug 25**: S0140-6736(23)01689-6. doi: 10.1016/S0140-6736(23)01689-6. PMID: 37640035. Steering committee, National Leader, and Coordinator. IF: 168.9; (Q1).

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- **Publicaciones como investigador colaborador en estudios internacionales**

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- **Otras publicaciones nacionales**

15. Alonso M, **Popova E**, et al. Study protocol for an observational cohort evaluating incidence and clinical relevance of perioperative elevation of high-sensitivity troponin I and N-terminal pro-brain natriuretic peptide in patients undergoing lung resection. **BMJ Open. 2022 Dec 8**;12(12): e063778. doi: 10.1136/bmjopen-2022-063778. PMID: 36600389. PMCID: PMC9743392. IF: 2.9; (Q1).

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- **Pertenencia a Comités científicos y/o asesores**

- Líder Nacional, Coordinador Nacional, (español), así como miembro del comité directivo de estudios multinacionales, multicéntricos promovidos por el *Population Health Research Institute* (PHRI), de *McMaster University, Hamilton*, Canadá.

- Grupo de trabajo de guías clínicas de la Sociedad Europea de Anestesiología y Cuidados Intensivos (*European Society of Anesthesiology and Intensive Care - ESAIC*).

- Junta Directiva de la Sociedad de Investigación y Cuidados Perioperatorios (*Society for Perioperative Research and Care -SPRC*).

EJA

Eur J Anaesthesiol 2023; **40:**888–927

INFOGRAPHIC

GUIDELINES

ESAIC focused guideline for the use of cardiac biomarkers in perioperative risk evaluation

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BACKGROUND In recent years, there has been increasing focus on the use of cardiac biomarkers in patients undergoing noncardiac surgery.

AIMS The aim of this focused guideline was to provide updated guidance regarding the pre-, post- and combined pre-and postoperative use of cardiac troponin and B-type natriuretic peptides in adult patients undergoing noncardiac surgery.

METHODS The guidelines were prepared using Grading of Recommendations Assessment Development and Evaluation (GRADE) methodology. This included the definition of critical outcomes, a systematic literature search, appraisal of certainty of evidence, evaluation of biomarker measurement in terms of the balance of desirable and undesirable effects including clinical outcomes, resource use, health inequality, stakeholder acceptance, and implementation. The panel differentiated between three different scopes of applications: cardiac biomarkers as prognostic factors, as tools for risk prediction, and for biomarker-enhanced management strategies.

RESULTS In a modified Delphi process, the task force defined 12 critical outcomes. The systematic literature search resulted in over 25,000 hits, of which 115 full-text articles formed the body of evidence for recommendations. The evidence appraisal indicated heterogeneity in the certainty of evidence across critical outcomes. Further, there was relevant gradient in the certainty of evidence across the three scopes of application. Recommendations were issued and if this was not possible due to limited evidence, clinical practice statements were produced.

CONCLUSION The ESAIC focused guidelines provide guidance on the perioperative use of cardiac troponin and B-type natriuretic peptides in patients undergoing noncardiac surgery, for three different scopes of application.

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OPEN

REVIEW ARTICLE

Expert consensus on peri-operative myocardial injury screening in noncardiac surgery

A literature review

Christian Puelacher, Bernardo Bollen Pinto, Nicholas L. Mills, Emmanuelle Duceppe, Ekaterine Popova, Andreas Duma, Peter Nagele, Torbjørn Omland, Angelika Hammerer-Lercher and Giovanna Lurati Buse

Peri-operative myocardial injury, detected by dynamic and elevated cardiac troponin (cTn) concentrations, is a common complication of noncardiac surgery that is strongly associated with 30-day mortality. Although active screening for peri-operative myocardial injury has been suggested in recent guidelines, clinical implementation remains tentative due to a lack of examples on how to tackle such an interdisciplinary project at a local level. Moreover, consensus on which assay and cTn cut-off values should be used has not yet been reached, and guidance on whom to screen is lacking. In this article, we aim to summarise local examples of successfully implemented cTn screening practices and review the current literature in order to provide information and suggestions for patient selection, organisation of a screening programme, caveats and a potential management pathway.

Published online 1 March 2021

Introduction

Every year, over 300 million surgical procedures are performed worldwide, with numbers steadily increasing. Recent evidence suggests that postoperative death accounts for 7.7% of global mortality and is the third leading cause of mortality worldwide.[1] In patients undergoing major noncardiac surgery, peri-operative mortality remains high during the first 30 days postsurgery.[2–4]

Myocardial infarction following noncardiac surgery has been shown to be associated with poor long-term outcomes.[5,6] According to the Universal Definition of Myocardial Infarction, acute myocardial infarction is diagnosed when acute myocardial injury, defined as dynamic and elevated cardiac troponin (cTn) with at least 1 value above the 99th percentile, is accompanied by clinical evidence of myocardial ischaemia (Table 1).[7]

Due to the high reliance of the Universal Definition on symptoms for the detection of myocardial infarction, something that might not be so apparent in the peri-operative setting due to sedation and analgesia, further studies were needed to systematically screen for peri-operative myocardial injury using cTn, the cornerstone of the Universal Definition.[8,9] These showed that peri-operative myocardial injury, detected by elevated and dynamic changes in cTn with or without additional

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Humble CAS, De Hert S, Chew MS. Expert consensus on peri-operative myocardial injury screening in noncardiac surgery. *Eur J Anaesthesiol* 2021; **38**:569–570.

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Effect of colchicine on perioperative atrial fibrillation and myocardial injury after non-cardiac surgery in patients undergoing major thoracic surgery (COP-AF): an international randomised trial

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Summary

Background Higher levels of inflammatory biomarkers are associated with an increased risk of perioperative atrial fibrillation and myocardial injury after non-cardiac surgery (MINS). Colchicine is an anti-inflammatory drug that might reduce the incidence of these complications.

Methods COP-AF was a randomised trial conducted at 45 sites in 11 countries. Patients aged 55 years or older and undergoing major non-cardiac thoracic surgery were randomly assigned (1:1) to receive oral colchicine 0·5 mg twice daily or matching placebo, starting within 4 h before surgery and continuing for 10 days. Randomisation was done with use of a computerised, web-based system, and was stratified by centre. Health-care providers, patients, data collectors, and adjudicators were masked to treatment assignment. The coprimary outcomes were clinically important perioperative atrial fibrillation and MINS during 14 days of follow-up. The main safety outcomes were a composite of sepsis or infection, and non-infectious diarrhoea. The intention-to-treat principle was used for all analyses. This trial is registered with ClinicalTrials.gov, NCT03310125.

Findings Between Feb 14, 2018, and June 27, 2023, we enrolled 3209 patients (mean age 68 years [SD 7], 1656 [51·6%] male). Clinically important atrial fibrillation occurred in 103 (6·4%) of 1608 patients assigned to colchicine, and 120 (7·5%) of 1601 patients assigned to placebo (hazard ratio [HR] 0·85, 95% CI 0·65 to 1·10; absolute risk reduction [ARR] 1·1%, 95% CI –0·7 to 2·8; p=0·22). MINS occurred in 295 (18·3%) patients assigned to colchicine and 325 (20·3%) patients assigned to placebo (HR 0·89, 0·76 to 1·05; ARR 2·0%, –0·8 to 4·7; p=0·16). The composite outcome of sepsis or infection occurred in 103 (6·4%) patients in the colchicine group and 83 (5·2%) patients in the placebo group (HR 1·24, 0·93–1·66). Non-infectious diarrhoea was more common in the colchicine group (134 [8·3%] events) than the placebo group (38 [2·4%]; HR 3·64, 2·54–5·22).

Interpretation In patients undergoing major non-cardiac thoracic surgery, administration of colchicine did not significantly reduce the incidence of clinically important atrial fibrillation or MINS but increased the risk of mostly benign non-infectious diarrhoea.

Funding Canadian Institutes of Health Research, Accelerating Clinical Trials Consortium, Innovation Fund of the Alternative Funding Plan for the Academic Health Sciences Centres of Ontario, Population Health Research Institute, Hamilton Health Sciences, Division of Cardiology at McMaster University, Canada; Hanela Foundation, Switzerland; and General Research Fund, Research Grants Council, Hong Kong.

Introduction

Colchicine is an inexpensive drug with anti-inflammatory effects.[1–3] Its efficacy has been shown in multiple inflammatory diseases, such as gout, pericarditis, and familial Mediterranean fever.[4–6] Results from small randomised trials suggest that in patients undergoing cardiac surgery, low-dose colchicine reduces the risk of postpericardiotomy syndrome and perioperative atrial fibrillation.[7–9] Two large randomised trials, Low Dose Colchicine 2 (LoDoCo2) and Colchicine Cardiovascular Outcomes Trial (COLCOT), found that low-dose colchicine significantly reduced the incidence of major cardiovascular outcomes in patients with coronary artery disease.[10,11]

Higher levels of inflammatory biomarkers have been associated with an increased risk of perioperative atrial fibrillation and myocardial injury after non-cardiac

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*A full list of the COP-AF Investigators is provided in the appendix (pp 2–4)

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Effect of Colchicine on the Risk of Perioperative Acute Kidney Injury: Clinical Protocol of a Substudy of the Colchicine for the Prevention of Perioperative Atrial Fibrillation Randomized Clinical Trial

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Abstract

Background: Inflammation during and after surgery can lead to organ damage including acute kidney injury. Colchicine, an established inexpensive anti-inflammatory medication, may help to protect the organs from pro-inflammatory damage. This protocol describes a kidney substudy of the colchicine for the prevention of perioperative atrial fibrillation (COP-AF) study, which is testing the effect of colchicine versus placebo on the risk of atrial fibrillation and myocardial injury among patients undergoing thoracic surgery.

Objective: Our kidney substudy of COP-AF will determine whether colchicine reduces the risk of perioperative acute kidney injury compared with a placebo. We will also examine whether colchicine has a larger absolute benefit in patients with pre-existing chronic kidney disease, the most prominent risk factor for acute kidney injury.

Design and Setting: Randomized, superiority clinical trial conducted in 40 centers in 11 countries from 2018 to 2023.

Patients: Patients (~3200) aged 55 years and older having major thoracic surgery.

Intervention: Patients are randomized 1:1 to receive oral colchicine (0.5 mg tablet) or a matching placebo, given twice daily starting 2 to 4 hours before surgery for a total of 10 days. Patients, health care providers, data collectors, and outcome adjudicators will be blinded to the randomized treatment allocation.

Methods: Serum creatinine concentrations will be measured before surgery and on postoperative days 1, 2, and 3 (or until hospital discharge). The primary outcome of the substudy is perioperative acute kidney injury, defined as an increase (from the prerandomization value) in serum creatinine concentration of either ≥26.5 μmol/L (≥0.3 mg/dL) within 48 hours of surgery or ≥50% within 7 days of surgery. The primary analysis (intention-to-treat) will examine the relative risk of acute kidney injury in patients allocated to receive colchicine versus placebo. We will repeat the primary analysis using alternative definitions of acute kidney injury and examine effect modification by pre-existing chronic kidney disease, defined as a prerandomization estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73 m^2.

Limitations: The substudy will be underpowered to detect small effects on more severe forms of acute kidney injury treated with dialysis.

Results: Substudy results will be reported in 2024.

Conclusions: This substudy will estimate the effect of colchicine on the risk of perioperative acute kidney injury in older adults undergoing major thoracic surgery.

Clinical trial registration number: NCT03310125

Trial Designs

Rationale and design of the colchicine for the prevention of perioperative atrial fibrillation in patients undergoing major noncardiac thoracic surgery (COP-AF) trial

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Background Perioperative atrial fibrillation (AF) and myocardial injury after noncardiac surgery (MINS) are common complications after noncardiac surgery. Inflammation has been implicated in the pathogenesis of both disorders. The COP-AF trial tests the hypothesis that colchicine reduces the incidence of perioperative AF and MINS in patients undergoing major noncardiac thoracic surgery.

Methods and Results The 'COlchicine for the Prevention of Perioperative Atrial Fibrillation' (COP-AF) trial is an international, blinded, randomized trial that compares colchicine to placebo in patients aged at least 55 years and undergoing major noncardiac thoracic surgery with general anesthesia. Exclusion criteria include a history of AF and a contraindication to colchicine (eg, severe renal dysfunction). Oral colchicine at a dose of 0.5 mg or matching placebo is given within 4 hours before surgery. Thereafter, patients receive colchicine 0.5 mg or placebo twice daily for a total of 10 days. The 2 independent co-primary outcomes are clinically important perioperative AF (including atrial flutter) and MINS during 14 days of follow-up. The main safety outcomes are sepsis or infection and non-infectious diarrhea. We aim to enroll

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AJKD

Accelerated Surgery Versus Standard Care in Hip Fracture (HIP ATTACK-1): A Kidney Substudy of a Randomized Clinical Trial

To the Editor:

Acute kidney injury (AKI) is a lesser-known complication of hip fracture that may come about owing to decreased kidney perfusion and heightened inflammation from trauma, pain, bleeding, and fasting.[1,2] Approximately 15%-20% of patients undergoing surgery for a hip fracture develop AKI, with 0.5%-1.8% receiving dialysis.[3-5] A strategy of accelerating the time to surgery after a hip fracture was recently compared with standard care in HIP ATTACK-1 (ClinicalTrials.gov identifier NCT02027896), a multinational randomized clinical trial.[6,7] Enrollment occurred March 2014 through May 2019, and 2,970 patients from 69 hospitals in 17 countries were randomized. Compared with standard care, accelerated medical assessment and surgical repair did not significantly lower the risk of the 2 co–primary outcomes (mortality and major perioperative complications), although it did decrease the risk of delirium, moderate-to-severe pain, and urinary tract infection, and resulted in faster mobilization and a shorter hospital stay.[7]

We conducted a prespecified kidney substudy of HIP ATTACK-1 to examine the effect of accelerated surgical treatment versus standard care on AKI in patients with a hip fracture.[8] Eligibility criteria for the main trial and the kidney substudy are provided in Table S1, and substudy methods are detailed in Item S1; minor changes in substudy execution compared to the published protocol[8] are summarized in Table S2. Briefly, eligible patients aged ≥45 years who presented to the emergency department with a hip fracture were randomly allocated (1:1) to receive accelerated surgical repair or standard care. The primary outcome of the substudy was AKI, defined as an Scr increase (from the prerandomization value) of ≥0.3 mg/dL (26.5 μmol/L) within 48 hours after randomization, or an increase of ≥50% within 7 days after randomization.[9] Six secondary definitions of AKI (listed in Item S1) were also examined.

Of 2,970 patients randomized in HIP ATTACK-1, 2,445 (82%) were included in the substudy (Figure S1). Baseline characteristics of patients in the substudy are shown in Table 1 (corresponding data for the main trial are in Table S3). The baseline, prerandomization Scr was obtained at the time of hospital admission for 99% of patients and before the hospital admission for 1%. The accelerated surgery group had surgery earlier than the standard care group and the mean between-group difference in the time from hip fracture diagnosis to surgery was 18 (95% CI, 15-20) hours.

AKI occurred in 13.5% (163/1,204) in the accelerated surgery group and in 14.9% (179/1,203) in the standard care group (postrandomization Scr was missing in 38 [1.6%] patients and was imputed using fully conditional specification for the primary analysis as described in Item S1). The relative risk (RR) was 0.91 (95% CI, 0.74-1.13), and the absolute risk difference was 1.3% (95% CI, −1.5% to 4.1%; Table 2). Results were similar in sensitivity analyses (Tables S4-S5). The mean between-group difference in the percentage and absolute change in Scr to the peak value was −1.5 (95% CI, −5.2 to 2.2) and −1.9 (95% CI, −5.1 to 1.3), respectively. The time to AKI after randomization in each group is shown in Figure S2. Pre-existing chronic kidney disease (CKD) did not significantly modify the effect of the accelerated surgery intervention versus standard care on AKI (Table S6), nor did prerandomization eGFR considered as a continuous variable ($P = 0.1$ for the interaction between the group allocation and eGFR).

The strengths of this substudy include its randomized concealed allocation, recruitment from 69 hospitals in 17 countries, and standardized collection of postrandomization Scr. Three limitations merit discussion. First, baseline Scr was obtained at the time of hospital admission for 99% of patients. Depending on the circumstances of the fracture, instability in the baseline measurement could complicate detecting an acute rise in postrandomization Scr, which is needed to identify AKI. That said, the average baseline Scr was 0.96 mg/dL, a level considered normal. Second, urine output data were not collected, given challenges with accurate measurement in an international setting. Third, we were underpowered to detect an RR reduction <30% for the primary AKI outcome. Therefore, we conducted prespecified analyses of the percentage change and the absolute change to the peak postrandomization Scr; however, no statistically significant between-group differences were observed.

In summary, the risk of perioperative AKI was not significantly different in patients allocated to accelerated surgery versus standard care for hip fracture. AKI occurred nearly twice as often in patients with versus without CKD (21% vs 11%); however, regardless of CKD status, the risk of AKI was not significantly lower with accelerated surgery versus standard care.

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Accelerated surgery versus standard care in hip fracture (HIP ATTACK): an international, randomised, controlled trial

*The HIP ATTACK Investigators**

Summary

Background Observational studies have suggested that accelerated surgery is associated with improved outcomes in patients with a hip fracture. The HIP ATTACK trial assessed whether accelerated surgery could reduce mortality and major complications.

Methods HIP ATTACK was an international, randomised, controlled trial done at 69 hospitals in 17 countries. Patients with a hip fracture that required surgery and were aged 45 years or older were eligible. Research personnel randomly assigned patients (1:1) through a central computerised randomisation system using randomly varying block sizes to either accelerated surgery (goal of surgery within 6 h of diagnosis) or standard care. The coprimary outcomes were mortality and a composite of major complications (ie, mortality and non-fatal myocardial infarction, stroke, venous thromboembolism, sepsis, pneumonia, life-threatening bleeding, and major bleeding) at 90 days after randomisation. Patients, health-care providers, and study staff were aware of treatment assignment, but outcome adjudicators were masked to treatment allocation. Patients were analysed according to the intention-to-treat principle. This study is registered at ClinicalTrials.gov (NCT02027896).

Findings Between March 14, 2014, and May 24, 2019, 27 701 patients were screened, of whom 7780 were eligible. 2970 of these were enrolled and randomly assigned to receive accelerated surgery (n=1487) or standard care (n=1483). The median time from hip fracture diagnosis to surgery was 6 h (IQR 4–9) in the accelerated-surgery group and 24 h (10–42) in the standard-care group (p<0·0001). 140 (9%) patients assigned to accelerated surgery and 154 (10%) assigned to standard care died, with a hazard ratio (HR) of 0·91 (95% CI 0·72 to 1·14) and absolute risk reduction (ARR) of 1% (–1 to 3; p=0·40). Major complications occurred in 321 (22%) patients assigned to accelerated surgery and 331 (22%) assigned to standard care, with an HR of 0·97 (0·83 to 1·13) and an ARR of 1% (–2 to 4; p=0·71).

Interpretation Among patients with a hip fracture, accelerated surgery did not significantly lower the risk of mortality or a composite of major complications compared with standard care.

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See Online for appendix

Introduction

Worldwide, more than 1·5 million adults have a hip fracture each year.[1] Non-surgical management of a hip fracture is associated with a low probability of remaining ambulatory and an increased risk of chronic pain and mortality.[2,3] In high-income countries, about 95% of hip fractures are managed surgically.[4,5] Patients undergoing hip fracture surgery have higher risk-adjusted mortality and major complications than patients undergoing elective total hip replacement surgery, suggesting hip fractures, independent of surgery, increase patients' risks.[6]

Patients who have a hip fracture are at substantial risk of major complications (ie, cardiovascular, infectious, bleeding, and neurocognitive) and mortality.[7–9] Observational studies suggest that accelerated surgery for a hip fracture is associated with a lower risk of mortality and major complications.[10,11] Hip fractures result in pain, bleeding, and immobility, and activate inflammatory, hypercoagulable, catabolic, and stress states that can precipitate medical complications.[12–15] Accelerated surgery will reduce the time patients are exposed to these harmful states and therefore might reduce the risk of medical complications and mortality. We did the hip fracture accelerated surgical treatment and care track (HIP ATTACK) trial to establish whether accelerated surgery for hip fracture was superior to standard care in reducing death or other major complications.

Methods

Study design and patients

We did this investigator-initiated, randomised, controlled trial at 69 hospitals in 17 countries (Canada, Spain, India, Pakistan, South Africa, Italy, Poland, the UK, the USA, Malaysia, Belgium, France, Thailand, the Netherlands, China, Hong Kong, and Colombia). We have previously reported details of the trial design and methods.[16,17] Before commencing recruitment, all centres obtained ethics approval, and the relevant health authorities approved the protocol.

Eligible patients were aged 45 years or older and diagnosed during regular working hours with a low-energy mechanism hip fracture that required surgery.

PERIOPERATIVE MEDICINE

ANESTHESIOLOGY

One-year Results of a Factorial Randomized Trial of Aspirin *versus* Placebo and Clonidine *versus* Placebo in Patients Having Noncardiac Surgery

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- The Perioperative Ischemic Evaluation-2 study (POISE-2) authors previously reported that neither aspirin nor clonidine reduced a 30-day composite of nonfatal myocardial infarction or death. Aspirin caused perioperative bleeding, and clonidine provoked hypotension and bradycardia.
- In a subgroup analysis of patients who had previous percutaneous coronary interventions, those given aspirin had fewer infarctions or deaths.

What This Article Tells Us That Is New

- This article reports 1-yr outcomes of the POISE-2 study. Consistent with the 30-day analysis, neither aspirin nor clonidine reduced a 1-yr composite of nonfatal myocardial infarction or death.
- In a subgroup analysis of patients who had prior percutaneous coronary interventions, those given aspirin had significantly fewer nonfatal myocardial infarctions and/or deaths.

ABSTRACT

Background: The authors previously reported that perioperative aspirin and/or clonidine does not prevent a composite of death or myocardial infarction 30 days after noncardiac surgery. Moreover, aspirin increased the risk of major bleeding and clonidine caused hypotension and bradycardia. Whether these complications produce harm at 1 yr remains unknown.

Methods: The authors randomized 10,010 patients with or at risk of atherosclerosis and scheduled for noncardiac surgery in a 1:1:1:1 ratio to clonidine/aspirin, clonidine/aspirin placebo, clonidine placebo/aspirin, or clonidine placebo/aspirin placebo. Patients started taking aspirin or placebo just before surgery; those not previously taking aspirin continued daily for 30 days, and those taking aspirin previously continued for 7 days. Patients were also randomly assigned to receive clonidine or placebo just before surgery, with the study drug continued for 72 h.

Results: Neither aspirin nor clonidine had a significant effect on the primary 1-yr outcome, a composite of death or nonfatal myocardial infarction, with a 1-yr hazard ratio for aspirin of 1.00 (95% CI, 0.89 to 1.12; $P = 0.948$; 586 patients [11.8%] *vs.* 589 patients [11.8%]) and a hazard ratio for clonidine of 1.07 (95% CI, 0.96 to 1.20; $P = 0.218$; 608 patients [12.1%] *vs.* 567 patients [11.3%]), with effect on death or nonfatal infarction. Reduction in death and nonfatal myocardial infarction from aspirin in patients who previously had percutaneous coronary intervention at 30 days persisted at 1 yr. Specifically, the hazard ratio was 0.58 (95% CI, 0.35 to 0.95) in those with previous percutaneous coronary intervention and 1.03 (95% CI, 0.91 to 1.16) in those without (interaction $P = 0.033$). There was no significant effect of either drug on death, cardiovascular complications, cancer, or chronic incisional pain at 1 yr (all $P > 0.1$).

Conclusions: Neither perioperative aspirin nor clonidine have significant long-term effects after noncardiac surgery. Perioperative aspirin in patients with previous percutaneous coronary intervention showed persistent benefit at 1 yr, a plausible sub-group effect.

(ANESTHESIOLOGY 2020; 132:692–701)

Intraoperative mortality is now rare,[1,2] but postoperative mortality and morbidity remain common.[3,4] Major bleeding and myocardial infarction are leading attributable causes of mortality in the 30 days after noncardiac surgery.[5]

Currently, there is no known safe way to prevent postoperative myocardial infarction.[6,7] β-Blockers prevent myocardial infarction after noncardiac surgery but increase the risk of stroke and death.[6] Avoiding nitrous oxide is ineffective.[7] Both clonidine and aspirin were attractive candidates to reduce perioperative myocardial infarction because they either reduce sympathetic nervous system activation and lower heart rate, or block platelet activation and clot formation. However, the large randomized Perioperative Ischemic Evaluation-2 (POISE-2) trial failed to confirm these hypotheses, as neither aspirin[9] nor clonidine[8] prevented myocardial infarction or death within 30 days of randomization. We did, however, demonstrate that a subgroup of patients, those with previous percutaneous coronary interventions, benefit from

Open access Protocol

BMJ Open

Rationale and design of the HIP fracture Accelerated surgical TreaTment And Care tracK (HIP ATTACK) Trial: a protocol for an international randomised controlled trial evaluating early surgery for hip fracture patients

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ABSTRACT

Introduction Annually, millions of adults suffer hip fractures. The mortality rate post a hip fracture is 7%–10% at 30 days and 10%–20% at 90 days. Observational data suggest that early surgery can improve these outcomes in hip fracture patients. We designed a clinical trial—HIP fracture Accelerated surgical TreaTment And Care tracK (HIP ATTACK) to determine the effect of accelerated surgery compared with standard care on the 90-day risk of all-cause mortality and major perioperative complications.

Methods and analysis HIP ATTACK is a multicentre, international, parallel group randomised controlled trial (RCT) that will include patients ≥45 years of age and diagnosed with a hip fracture from a low-energy mechanism requiring surgery. Patients are randomised to accelerated medical assessment and surgical repair (goal within 6 h) or standard care. The co-primary outcomes are (1) all-cause mortality and (2) a composite of major perioperative complications (ie, mortality and non-fatal myocardial infarction, pulmonary embolism, pneumonia, sepsis, stroke, and life-threatening and major bleeding) at 90 days after randomisation. All patients will be followed up for a period of 1 year. We will enrol 3000 patients.

Ethics and dissemination All centres had ethics approval before randomising patients. Written informed consent is required for all patients before randomisation. HIP ATTACK is the first large international trial designed to examine whether accelerated surgery can improve outcomes in patients with a hip fracture. The dissemination plan includes publishing the results in a policy-influencing journal, conference presentations, engagement of influential medical organisations, and providing public awareness through multimedia resources.

Trial registration number NCT02027896; Pre-results.

Strengths and limitations of this study

- HIP fracture Accelerated surgical TreaTment And Care tracK (HIP ATTACK) is the first large randomised controlled trial powered to determine the effects of accelerated surgery compared with the standard of care in hip fracture patients.
- HIP ATTACK trial implemented patient engagement strategies, including research governance, trial outcome evaluation and knowledge translation.
- Patients, healthcare providers and study personnel are unblinded to patient treatment allocation; however, outcome adjudicators are blinded to treatment allocation.
- HIP ATTACK will only inform the effect of accelerated surgery versus standard care during hospital working hours and does not inform the effects outside of working hours.

INTRODUCTION

Worldwide, millions of adults suffer a hip fracture annually.[1] A hip fracture results in trauma, pain, bleeding and immobility. These

Original article

Effect of aspirin in vascular surgery in patients from a randomized clinical trial (POISE-2)

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Background: In the POISE-2 (PeriOperative ISchemic Evaluation 2) trial, perioperative aspirin did not reduce cardiovascular events, but increased major bleeding. There remains uncertainty regarding the effect of perioperative aspirin in patients undergoing vascular surgery. The aim of this substudy was to determine whether there is a subgroup effect of initiating or continuing aspirin in patients undergoing vascular surgery.

Methods: POISE-2 was a blinded, randomized trial of patients having non-cardiac surgery. Patients were assigned to perioperative aspirin or placebo. The primary outcome was a composite of death or myocardial infarction at 30 days. Secondary outcomes included: vascular occlusive complications (a composite of amputation and peripheral arterial thrombosis) and major or life-threatening bleeding.

Results: Of 10 010 patients in POISE-2, 603 underwent vascular surgery, 319 in the continuation and 284 in the initiation stratum. Some 272 patients had vascular surgery for occlusive disease and 265 had aneurysm surgery. The primary outcome occurred in 13·7 per cent of patients having aneurysm repair allocated to aspirin and 9·0 per cent who had placebo (hazard ratio (HR) 1·48, 95 per cent c.i. 0·71 to 3·09). Among patients who had surgery for occlusive vascular disease, 15·8 per cent allocated to aspirin and 13·6 per cent on placebo had the primary outcome (HR 1·16, 0·62 to 2·17). There was no interaction with the primary outcome for type of surgery ($P = 0·294$) or aspirin stratum ($P = 0·623$). There was no interaction for vascular occlusive complications ($P = 0·413$) or bleeding ($P = 0·900$) for vascular compared with non-vascular surgery.

Conclusion: This study suggests that the overall POISE-2 results apply to vascular surgery. Perioperative withdrawal of chronic aspirin therapy did not increase cardiovascular or vascular occlusive complications. Registration number: NCT01082874 (http://www.clinicaltrials.gov).

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Introduction

The POISE-2 trial randomized 10 010 patients undergoing non-cardiac surgery who were either already taking aspirin (continuation stratum) or not (initiation stratum) to receive aspirin or placebo during the perioperative phase[1]. The trial demonstrated no benefit from low-dose perioperative aspirin in reducing cardiovascular events within 30 days of

Dabigatran in patients with myocardial injury after non-cardiac surgery (MANAGE): an international, randomised, placebo-controlled trial

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Summary

Background Myocardial injury after non-cardiac surgery (MINS) increases the risk of cardiovascular events and deaths, which anticoagulation therapy could prevent. Dabigatran prevents perioperative venous thromboembolism, but whether this drug can prevent a broader range of vascular complications in patients with MINS is unknown. The MANAGE trial assessed the potential of dabigatran to prevent major vascular complications among such patients.

Methods In this international, randomised, placebo-controlled trial, we recruited patients from 84 hospitals in 19 countries. Eligible patients were aged at least 45 years, had undergone non-cardiac surgery, and were within 35 days of MINS. Patients were randomly assigned (1:1) to receive dabigatran 110 mg orally twice daily or matched placebo for a maximum of 2 years or until termination of the trial and, using a partial 2-by-2 factorial design, patients not taking a proton-pump inhibitor were also randomly assigned (1:1) to omeprazole 20 mg once daily, for which results will be reported elsewhere, or matched placebo to measure its effect on major upper gastrointestinal complications. Research personnel randomised patients through a central 24 h computerised randomisation system using block randomisation, stratified by centre. Patients, health-care providers, data collectors, and outcome adjudicators were masked to treatment allocation. The primary efficacy outcome was the occurrence of a major vascular complication, a composite of vascular mortality and non-fatal myocardial infarction, non-haemorrhagic stroke, peripheral arterial thrombosis, amputation, and symptomatic venous thromboembolism. The primary safety outcome was a composite of life-threatening, major, and critical organ bleeding. Analyses were done according to the intention-to-treat principle. This trial is registered with ClinicalTrials.gov, number NCT01661101.

Findings Between Jan 10, 2013, and July 17, 2017, we randomly assigned 1754 patients to receive dabigatran (n=877) or placebo (n=877); 556 patients were also randomised in the omeprazole partial factorial component. Study drug was permanently discontinued in 401 (46%) of 877 patients allocated to dabigatran and 380 (43%) of 877 patients allocated to placebo. The composite primary efficacy outcome occurred in fewer patients randomised to dabigatran than placebo (97 [11%] of 877 patients assigned to dabigatran *vs* 133 [15%] of 877 patients assigned to placebo; hazard ratio [HR] 0·72, 95% CI 0·55–0·93; p=0·0115). The primary safety composite outcome occurred in 29 patients (3%) randomised to dabigatran and 31 patients (4%) randomised to placebo (HR 0·92, 95% CI 0·55–1·53; p=0·76).

Interpretation Among patients who had MINS, dabigatran 110 mg twice daily lowered the risk of major vascular complications, with no significant increase in major bleeding. Patients with MINS have a poor prognosis; dabigatran 100 mg twice daily has the potential to help many of the 8 million adults globally who have MINS to reduce their risk of a major vascular complication.

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See **Comment** page 2297

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Introduction

Myocardial injury after non-cardiac surgery (MINS) includes myocardial infarction and isolated ischaemic troponin elevation occurring within 30 days after surgery,[1] but does not include perioperative myocardial injury due to non-ischaemic causes (eg, sepsis, rapid atrial fibrillation, pulmonary embolism, and chronically elevated troponin measurement).[2] Without routine perioperative troponin measurements, more than 80% of MINS events would go unrecognised, because these patients do not have ischaemic symptoms.[1–3] A proposed explanation for these asymptomatic events is

ELSEVIER

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Clinical Research

Design of a Randomized Placebo-Controlled Trial to Assess Dabigatran and Omeprazole in Patients with Myocardial Injury after Noncardiac Surgery (MANAGE)

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ABSTRACT

Background: Worldwide approximately 200 million adults undergo major surgery annually, of whom 8 million are estimated to suffer a myocardial injury after noncardiac surgery (MINS). There is currently no trial data informing the management of MINS. Antithrombotic agents

RÉSUMÉ

Contexte : Chaque année à l'échelle mondiale, une intervention chirurgicale majeure est pratiquée chez environ 200 millions d'adultes. De ce nombre, quelque 8 millions subissent une lésion myocardique après une intervention chirurgicale non cardiaque

Myocardial injury represents the leading cause of death after major noncardiac surgery.[1,2] Annually, approximately 8% of the 200 million adults globally who undergo major surgery will suffer a myocardial injury.[3,4] Large international clinical studies have shown that myocardial injury after noncardiac surgery (MINS) is independently associated with 30-day (adjusted hazard ratio [HR], > 2.5)[1,2] and 1-year all-cause

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See page 7 for disclosure information.

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PERIOPERATIVE MEDICINE

ANESTHESIOLOGY

One-year Outcomes after Discharge from Noncardiac Surgery and Association between Predischarge Complications and Death after Discharge: Analysis of the VISION Prospective Cohort Study

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ABSTRACT

Background: In previous analyses, myocardial injury after noncardiac surgery, major bleeding, and sepsis were independently associated with most deaths in the 30 days after noncardiac surgery, but most of these deaths occurred during the index hospitalization for surgery. The authors set out to describe outcomes after discharge from hospital up to 1 yr after inpatient noncardiac surgery and associations between predischarge complications and postdischarge death up to 1 yr after surgery.

Methods: This study was an analysis of patients discharged after inpatient noncardiac surgery in a large international prospective cohort study across 28 centers from 2007 to 2013 of patients aged 45 yr or older followed to 1 yr after surgery. The study estimated (1) the cumulative postdischarge incidence of death and other outcomes up to a year after surgery and (2) the adjusted time-varying associations between postdischarge death and predischarge complications including myocardial injury after noncardiac surgery, major bleeding, sepsis, infection without sepsis, stroke, congestive heart failure, clinically important atrial fibrillation or flutter, amputation, venous thromboembolism, and acute kidney injury managed with dialysis.

Results: Among 38,898 patients discharged after surgery, the cumulative 1-yr incidence was 5.8% (95% CI, 5.5 to 6.0%) for all-cause death and 24.7% (95% CI, 24.2 to 25.1%) for all-cause hospital readmission. Predischarge complications were associated with 33.7% (95% CI, 27.2 to 40.2%) of deaths up to 30 days after discharge and 15.0% (95% CI, 12.0 to 17.9%) up to 1 yr. Most of the association with death was due to myocardial injury after noncardiac surgery (15.6% [95% CI, 9.3 to 21.9%] of deaths within 30 days, 6.4% [95% CI, 4.1 to 8.7%] within 1 yr), major bleeding (15.0% [95% CI, 8.3 to 21.7%] within 30 days, 4.7% [95% CI, 2.2 to 7.2%] within 1 yr), and sepsis (5.4% [95% CI, 2.2 to 8.6%] within 30 days, 2.1% [95% CI, 1.0 to 3.1%] within 1 yr).

Conclusions: One in 18 patients 45 yr old or older discharged after inpatient noncardiac surgery died within 1 yr, and one quarter were readmitted to the hospital. The risk of death associated with predischarge perioperative complications persists for weeks to months after discharge.

(ANESTHESIOLOGY 2024; 140:8–24)

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Previous literature demonstrates that myocardial injury after noncardiac surgery, major bleeding, and sepsis are independently associated with most deaths in the 30 days after noncardiac surgery, but most of these deaths typically occur during the index hospitalization for surgery
- It is unclear to what extent complications during the index hospitalization are associated with postdischarge death up to 1 yr after surgery

What This Article Tells Us That Is New

- In a secondary analysis of a prospective cohort study of 38,898 patients across 28 hospitals aged 45 yr or older who had inpatient noncardiac surgery between 2007 and 2013 and survived to hospital discharge, 2,165 (5.6%; cumulative incidence, 5.8%) patients died within 1 yr after surgery
- Complications during the index hospitalization were associated with 33.7% (95% CI, 27.2 to 40.2%) of deaths up to 30 days after discharge and 15.0% (95% CI, 12.0 to 17.9%) of deaths up to 1 yr after discharge
- Myocardial injury (6.4%), major bleeding (4.7%), and sepsis (2.1%) were associated with the most deaths within 1 yr

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

High-Sensitivity Troponin I after Cardiac Surgery and 30-Day Mortality

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ABSTRACT

BACKGROUND

Consensus recommendations regarding the threshold levels of cardiac troponin elevations for the definition of perioperative myocardial infarction and clinically important periprocedural myocardial injury in patients undergoing cardiac surgery range widely (from >10 times to ≥70 times the upper reference limit for the assay). Limited evidence is available to support these recommendations.

METHODS

We undertook an international prospective cohort study involving patients 18 years of age or older who underwent cardiac surgery. High-sensitivity cardiac troponin I measurements (upper reference limit, 26 ng per liter) were obtained 3 to 12 hours after surgery and on days 1, 2, and 3 after surgery. We performed Cox analyses using a regression spline that explored the relationship between peak troponin measurements and 30-day mortality, adjusting for scores on the European System for Cardiac Operative Risk Evaluation II (which estimates the risk of death after cardiac surgery on the basis of 18 variables, including age and sex).

RESULTS

Of 13,862 patients included in the study, 296 (2.1%) died within 30 days after surgery. Among patients who underwent isolated coronary-artery bypass grafting or aortic-valve replacement or repair, the threshold troponin level, measured within 1 day after surgery, that was associated with an adjusted hazard ratio of more than 1.00 for death within 30 days was 5670 ng per liter (95% confidence interval [CI], 1045 to 8260), a level 218 times the upper reference limit. Among patients who underwent other cardiac surgery, the corresponding threshold troponin level was 12,981 ng per liter (95% CI, 2673 to 16,591), a level 499 times the upper reference limit.

CONCLUSIONS

The levels of high-sensitivity troponin I after cardiac surgery that were associated with an increased risk of death within 30 days were substantially higher than levels currently recommended to define clinically important periprocedural myocardial injury. (Funded by the Canadian Institutes of Health Research and others; VISION Cardiac Surgery ClinicalTrials.gov number, NCT01842568.)

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Open access Protocol

BMJ Open

Study protocol for an observational cohort evaluating incidence and clinical relevance of perioperative elevation of high-sensitivity troponin I and N-terminal pro-brain natriuretic peptide in patients undergoing lung resection

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ABSTRACT

Introduction Myocardial injury after non-cardiac surgery has been defined as myocardial injury due to ischaemia, with or without additional symptoms or ECG changes occurring during or within 30 days after non-cardiac surgery and mainly diagnosed based on elevated postoperative cardiac troponin (cTn) values. In patients undergoing thoracic surgery for lung resection, only postoperative cTn elevations are seemingly not enough as an independent predictor of cardiovascular complications. After lung resection, troponin elevations may be regulated by mechanisms other than myocardial ischaemia. The combination of perioperative natriuretic peptide measurement together with high-sensitivity cTns may help to identify changes in ventricular function during thoracic surgery. Integrating both cardiac biomarkers may improve the predictive value for cardiovascular complications after lung resection. We designed our cohort study to evaluate perioperative elevation of both high-sensitivity troponin I (hs-TnI) and N-terminal pro-brain natriuretic peptide (NT-proBNP) in patients undergoing lung resection and to establish a risk score for major cardiovascular postoperative complications.

Methods and analysis We will conduct a prospective, multicentre, observational cohort study, including 345 patients undergoing elective thoracic surgery for lung resection. Cardiac biomarkers such as hs-TnI and NT-proBNP will be measured preoperatively and at postoperatively on days 1 and 2. We will calculate a risk score for major cardiovascular postoperative complications based on both biomarkers' perioperative changes. All patients will be followed up for 30 days after surgery.

Ethics and dissemination All participating centres were approved by the Ethics Research Committee. Written informed consent is required for all patients before inclusion. Results will be disseminated through publication in peer-reviewed journals and presentations at national or international conference meetings.

Trial registration number NCT04749212.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first study to integrate serial measurement of N-terminal pro-brain natriuretic peptide (NT-proBNP) and high-sensitivity troponin I (hs-TnI) biomarkers, more sensitive and specific for early detection of cardiovascular complications after lung resection.
⇒ The hs-TnI assay used in our study is more sensitive and accurate to detect low concentrations, contributing to a probable increase in detection of myocardial injury after non-cardiac surgery (MINS) than detected with conventional cardiac troponin assays.
⇒ Determining the clinical significance of hs-TnI elevation (due to ischaemic or non-ischaemic causes) may be crucial in the development of diagnostic and therapeutic protocols, aimed at improving MINS prognosis in patients undergoing thoracic surgery for lung resection.
⇒ The results of our study may be difficult to compare with previously published works, due to differences in methodology, especially when using both a hs-TnI assay, together with NT-proBNP.
⇒ Our protocol is designed as a short-term (30 days follow-up) study, therefore, long-term studies for better understanding of NT-proBNP and hs-TnI efficiency will be still needed.

INTRODUCTION

Myocardial injury is usually presented as acute coronary syndrome, manifested as myocardial infarction (MI) or unstable angina, and associated with symptoms as chest pain or shortness of breath.[1] However, perioperative myocardial injury after non-cardiac surgery (MINS), apparently triggered by myocardial

Open access Original research

BMJ Open

Preoperative clinical model to predict myocardial injury after non-cardiac surgery: a retrospective analysis from the MANAGE cohort in a Spanish hospital

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ABSTRACT

Objectives To determine preoperative factors associated to myocardial injury after non-cardiac surgery (MINS) and to develop a prediction model of MINS.

Design Retrospective analysis.

Setting Tertiary hospital in Spain.

Participants Patients aged ≥45 years undergoing major non-cardiac surgery and with at least two measures of troponin levels within the first 3 days of the postoperative period. All patients were screened for the MANAGE trial.

Primary and secondary outcome measures We used multivariable logistic regression analysis to study risk factors associated with MINS and created a score predicting the preoperative risk for MINS and a nomogram to facilitate bed-side use. We used Least Absolute Shrinkage and Selection Operator method to choose the factors included in the predictive model with MINS as dependent variable. The predictive ability of the model was evaluated. Discrimination was assessed with the area under the receiver operating characteristic curve (AUC) and calibration was visually assessed using calibration plots representing deciles of predicted probability of MINS against the observed rate in each risk group and the calibration-in-the-large (CITL) and the calibration slope. We created a nomogram to facilitate obtaining risk estimates for patients at pre-anaesthesia evaluation.

Results Our cohort included 3633 patients recruited from 9 September 2014 to 17 July 2017. The incidence of MINS was 9%. Preoperative risk factors that increased the risk of MINS were age, American Status Anaesthesiology classification and vascular surgery. The predictive model showed good performance in terms of discrimination (AUC=0.720; 95% CI: 0.69 to 0.75) and calibration slope=1.043 (95% CI: 0.90 to 1.18) and CITL=0.00 (95% CI: −0.12 to 0.12).

Conclusions Our predictive model based on routinely preoperative information is highly affordable and might be a useful tool to identify moderate-high risk patients before surgery. However, external validation is needed before implementation.

Strengths and limitations of this study

- ► The main strength of the present study is its large sample size.
- ► The simplicity and transposability of our predictive model allow its implementation worldwide.
- ► The main limitation is its unicentric setting, so our model needs external validation.
- ► The absence of preoperative troponin levels measurements may have favoured the inclusion of patients with chronically elevated troponin.
- ► Retrospective analysis and recollection of some data values in our study entail the usual limitations of observational studies with regard to potential confounders.

INTRODUCTION

Perioperative cardiovascular (CV) events are the leading cause of morbidity and mortality in patients undergoing major non-cardiac surgery.[1] These events include cardiac death, acute myocardial infarction, cardiogenic pulmonary oedema, ventricular fibrillation, cardiac arrest and complete heart block. Preoperative risk estimation of CV events is based on validated models. Among them, the Revised Cardiac Risk Index[2] (RCRI) has been widely used over the last 20 years probably due to its simplicity. The increasing availability of more specific and sensitive myocardial injury biomarkers,[3] together with a deeper understanding of the pathophysiology of myocardial injury after major non-cardiac surgery (MINS), has paved the way to the recognition as a specific entity.[4] The pathophysiology of MINS is multifactorial. Plaque rupture and mismatch between oxygen supply and

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Editorial

Myocardial Injury After Noncardiac Surgery. Could Dabigatran Be a First Step in Its Management?

Lesión miocárdica tras la cirugía no cardiaca: ¿el dabigatrán puede ser un primer paso para su tratamiento?

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Myocardial injury after noncardiac surgery (MINS), the most frequent cardiovascular complication after a surgical intervention, has a major prognostic impact.[1] Its effects can be powerfully illustrated using the following statistic: 1 in 10 patients with MINS will die within 30 days after surgery.[2] Given that 200 million patients worldwide undergo noncardiac surgery every year[3] and that the incidence of MINS varies between 15% and 18% according to the series consulted,[4,5] MINS is one of the main conditions affecting mortality in this setting. This relatively "young" entity was defined for the first time by the researchers of the VISION study,[6] which involved an international prospective cohort and evaluation of the major vascular complications in patients undergoing noncardiac surgery. They defined MINS as "all troponin elevations considered ischemic in origin, with prognostic relevance and occurring either during surgery or in the following 30 days". The VISION study revealed that almost 85% of patients with MINS do not show symptoms compatible with myocardial ischemia and that about two-thirds have no detectable electrocardiographic changes. Accordingly, this complication is usually missed by clinicians. Consequently, both the universal definition of infarction[7] and the main perioperative care guidelines now recommend the systematic and perioperative determination of troponin levels in patients with high cardiovascular risk.[8,9]

One of the most debated aspects, particularly within the cardiology community, is how patients with MINS should be managed. In terms of prevention, all attempts to extrapolate the robust advantages of drug therapies from nonsurgical cardiovascular medicine to the noncardiac surgery field have thus far failed. From the administration of beta-blockers[10] to antiplatelet monotherapy,[11] any hypothesized benefit has been rejected due to a lack of efficacy and even increases in severe postoperative complications such as stroke or bleeding. From the therapeutic point of view, no randomized studies have specifically attempted to answer this question. The available evidence has been observational and indicated that the use of aspirin and statins in patients who experience a perioperative infarction is associated with lower 30-day mortality.[12] However, the results of the MANAGE study were recently published.[13] This clinical trial is the first to attempt to determine whether administration of a direct anticoagulant (dabigatran) reduces the occurrence of cardiovascular complications in patients who experience MINS.

The MANAGE study is a multicenter, international clinical trial involving 84 hospitals in 19 countries around the world. The trial randomized 1754 patients in a factorial design to receive the following treatments for a maximum of 2 years or until the end of the study: dabigatran and omeprazole, dabigatran and placebo, placebo and omeprazole, or double placebo. The general hypothesis was that dabigatran would reduce cardiovascular complications and that omeprazole would minimize the risk of bleeding in patients who had undergone major noncardiac surgery and experienced MINS. Here, we report and discuss the results from the dabigatran group.

The inclusion criteria were as follows: patients aged $\geq$ 45 years who had undergone noncardiac surgery and met the universal definition of myocardial infarction valid at that time or had a postoperative troponin elevation with no explanation except myocardial ischemia (eg, sepsis, rapid atrial fibrillation, pulmonary embolism, or chronic troponin elevation).[14] Notably, preoperative determination of troponin levels was not required because its measurement is not routine clinical practice.

In addition, individuals with a history of coagulopathy or major bleeding or requiring therapeutic anticoagulation (eg, those with a cardiac prosthesis) were excluded. Patients were also excluded if the following persisted beyond 35 days after MINS onset: the attending surgeon considered that anticoagulation initiation represented undue risk or a physician considered that the patient needed prophylactic-dose anticoagulation to avoid a thromboembolism due to insufficient physical measures; dual antiplatelet therapy was required or the estimated glomerular filtration rate was $<$ 35 mL/min; and, finally, coronary angiography was considered necessary as a result of MINS.

Once included, patients were randomized to receive dabigatran 110 mg/twice daily or placebo. The primary efficacy outcome was a composite of vascular death, nonfatal myocardial infarction, nonhemorrhagic stroke, and peripheral arterial thrombosis. Given the low number of patients enrolled in the study, together with

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STUDY PROTOCOL

Rationale and design of perioperative myocardial ischemia: a protocol for troponin monitoring, prognostic thresholds, economic analysis and further insights into pathophysiology for non-cardiac surgery patients [version 1; peer review: 1 approved, 1 approved with reservations]

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Abstract

Introduction: Worldwide, near 200 million adults undergo major non cardiac surgery each year, and 10 million of them are estimated to suffer a myocardial injury after non-cardiac surgery (MINS), defined as an elevated high sensitive troponin T (hs-cTnT) in the first 3 days after surgery. Troponin levels need to be monitored in order to diagnose MINS, high sensitive cardiac Troponin T (hs-cTnT) assays being currently the most frequently used. Perioperative hs-cTnT screening could lead to care decisions that can potentially improve clinical outcomes. However, many of the clinical and economic implications of perioperative hs-cTnT monitoring remain unclear, and need to be elucidated.

Methods and analysis: Prospective cohort that will include patients

Open Peer Review

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