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2024 - Pros and cons in general internal medicine and geriatrics

Domenico Cucinotta

Former Chairman of the Department of Internal Medicine and Aging, University Hospital Bologna, Italy; Advisor and Professor, Master of Geriatric Medicine, San Marino and Ferrara Universities

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The obsession of longevity: Trying to stay healthy into old age is a better goal than attempting to live as long as possible

Despite an increase in lifespan over the last century, most people spend the extra years in poor health. Undoubtedly, older patients will rise to the overall majority of patients accessing social and healthcare systems unprepared to respond to special and complex demands. The future must transform significantly, emphasising a healthier and more active aging process. Trying to stay healthy into old age is a better goal than attempting to live as long as possible (1).

Some longevity influencers have gained notoriety by claiming they can radically extend human life with experimental drugs or laborious diet, exercise, and supplement protocols. But most experts who study aging are trying to target the second variable: not our life spans, but our "health spans," the number of years a person lives without serious disease, particularly those related to aging. There are currently two main ways experts think we can extend our health spans.

The first is by adopting everyday healthy behaviors, such as regular exercise, eating nutritious food, getting good sleep, and investing in our social bonds. The second is using more experimental approaches that target cellular processes involved with aging through drugs, genetic manipulations, or extreme diets.

These interventions have been shown to lengthen the lives of worms and mice. but it would take decades and billions of dollars to determine whether they can help humans live longer, too.

A more realistic goal is to stay healthy into old age and attempt to live as long as possible (2,3).

Life's essential 8 scores and poor brain health outcomes in middle-aged adults

Mounting evidence points to a strong connection between cardiovascular risk during middle age and brain health later in life. A two-stage (discovery and replication) prospective study was conducted in the United Kingdom and the United States, respectively. The primary exposure was the LE8 score, a validated tool that captures 8 modifiable cardiovascular risk factors (blood pressure, glucose, cholesterol, body mass index, smoking, physical activity, diet, and sleep duration), organised in 3 categories (optimal, intermediate, and poor). The primary outcome was a composite of stroke, dementia, or late-life depression. Among middle-aged adults, poor cardiovascular health profiles were associated with a two-fold higher risk of developing a composite outcome that captures the most critical diseases related to poor brain health. Because the evaluated risk factors are all modifiable, the findings of this study highlight the potential brain health benefits of using Life's Essential 8 to guide cardiovascular health optimization (4).

Novel advanced brain imaging technique reveals complex blood flow patterns in microscopic detail.

Scientists have developed a revolutionary optical imaging technique that provides unprecedented views of blood vessels in the living brain, offering new ways to study neurological conditions like stroke and Alzheimer's disease. Mapping the brain's blood supply is based on an advanced microscopy system that can capture detailed three-dimensional images of blood vessels in the brain while measuring blood flow velocities across thousands of vessels. The breakthrough technology, called extended-focus optical coherence microscopy, provides a comprehensive view of the brain's vascular network from its largest vessels down to its tiniest capillaries.

The new system uses a specially designed "Bessel beam" to extend the microscope's focus, allowing it to image much larger brain tissue sections than conventional methods. Unlike traditional approaches that either look at tiny volumes or lose detail over larger areas, this technique maintains high resolution across a substantial viewing area of 1000 × 1000 × 360 micrometres. Integrating high-sensitivity Doppler optical coherence tomography with advanced data processing algorithms makes it possible to precisely measure blood flow velocities and directions across thousands of brain vessels. Artificial intelligence is also incorporated into the system. A deep learning algorithm helps accurately identify and trace blood vessels throughout the captured volume, while sophisticated processing techniques determine blood flow direction and velocity in each vessel. Blood flow velocity varies significantly across different types of vessels. The team found that pial arteries, which sit on the brain's surface, exhibit the highest flow velocities of up to 30 mm/s while accounting for 21% of the total blood volume.

This new imaging capability has important implications for studying various neurological conditions. In Alzheimer's disease, for instance, changes in brain blood flow can occur long before other symptoms appear. Similarly, in stroke research, the technique could provide valuable insights into how blood flow changes in affected brain regions and how potential treatments might influence recovery. The ability to visualize these changes in an intact living brain marks a significant advancement in neurological research. and the technology could also be applied to studying blood flow in other organs, potentially advancing vascular research across multiple medical fields and representing a significant step forward in studying the brain's vascular system in unprecedented detail.

In brief, the research represents a significant step forward in our ability to study the brain's vascular system in unprecedented detail. Providing both structural and functional information about blood vessels at multiple scales opens new possibilities for understanding and treating various neurological conditions and could lead to new therapeutic strategies (5).

Cerebral blood flow (CBF) and arterial transit time (ATT)

Cerebral blood flow (CBF) and arterial transit time (ATT) are markers of brain vascular health. It is well established that CBF declines with age. Age-related cerebral atrophy and/or reductions in cerebral metabolic rate are hypothesised to explain CBF declines. Several researchers in older adults have identified some modifiable risk factors that can be addressed with simple lifestyle changes, such as: physical activity, social interaction, body weight/composition, and cardiovascular health. Results found that being overweight was associated with lower global CBF and a longer global ATT. Although the impact of weight loss interventions on ATT warrants further investigation, in overweight and obese middle-aged adults weight loss appears to increase CBF across large brain regions.

In older adults, conflicting findings regarding the association between cardiorespiratory fitness and CBF have been reported. However, cardiorespiratory fitness appears to have little effect on CBF. Still, it may induce longer ATT in specific regions, thus improving gas exchange and oxygen extraction fraction that could help explain the preservation of cerebral tissue integrity and cognition that is associated with regular exercise training. Nevertheless, the responses of CBF and ATT to exercise training warrant further investigation before making robust conclusions (6).

Frailty phenotypes and their association with health consequences

The frailty index is widely used in clinical and community settings to assess health status in older adults. Still, it can fail to identify the potential phenotypes or their relationship with health consequences. The 11-year follow-up data from the Taiwan Longitudinal Study on Aging, identified three frailty phenotypes: energy-based frailty (EBF), sarcopenia-based frailty (SBF), and hybrid-based frailty (HBF). Existing frailty measures such as the study of osteoporotic fractures (SOF),fatigue, resistance, ambulation, illness, loss of weight (FRAIL), and Fried scales were applied, to examine their correlation with health outcomes, such as falls and fractures, depression, comorbidities, hospitalization, emergency department visits, and mortality, adjusting for individual-level characteristics.

Older adults with only EBF were found to be at a lower risk of falls and fractures than their counterparts with only SBF. Depression was less likely in the SBF group than in the EBF group. Hybrid-based frail older adults were more likely to be hospitalized and have emergency department visits.

The proposed frailty phenotype classification differs from the existing frailty measures in its ability to distinguish the corresponding phenotypes underlying various health consequences. Strategies based on frailty phenotypes could mitigate adverse health consequences and should be a good usual clinical practice in the care of older patients (7).

Targeting sarcopenia

Sarcopenia is becoming more common as the world's population ages, and it has been noted that this condition reduces quality of life. The European Working Group of Sarcopenia in older people has emphasized the significance of evaluating muscle mass and muscle quality as a diagnostic criterion for sarcopenia (8).

The extracellular water-to-total body water ratio (ECW/TBW), measured using bioelectrical impedance analysis (BIA), has recently received attention as an indicator of muscle quality. However, the influence of aging on the ECW/TBW remains unclear.

A recent cross-sectional study included 237 community-dwelling females aged 20-89 years who could perform activities of daily living independently. ECW/TBW and skeletal muscle index (SMI) were measured using BIA. Multiple linear regression analyses of ECW/TBW and SMI were conducted. Age, body mass index (BMI), number of medications, pain, and medical history were considered independent variables. In the multiple linear regression analysis, age was significantly and independently associated with ECW/TBW and SMI. When the participants were divided into groups based on age, an increase in ECW/TBW and a decrease in SMI in the 65-89-year group were confirmed (8).

In summary, this study revealed that ECW/TBW increases with aging in community-dwelling females. Assessing muscle mass alone may not be adequate to capture the influences of aging on muscle composition, and evaluating ECW/TBW may be crucial for diagnosing sarcopenia. Although muscle mass, muscle strength, and functional performance typically serve as the primary endpoints for starting therapeutical treatments, of ECW/TBW can help target sarcopenia.

Is aspirin safe and effective for prevention?

No single trial has provided conclusive evidence that long-term administration of aspirin is safe and effective, either in primary prevention or in chronic atherosclerotic cardiovascular disease (ASCVD). Decades of recommendations to give aspirin for primary prevention of cardiovascular events, based on over-optimistic interpretation of inconclusive data, were recently overturned after a randomized clinical trial with approximately 100,000 person-years of follow-up where aspirin increased all-cause mortality. Several other primary prevention trials of aspirin also failed to show meaningful reductions in cardiovascular events. Furthermore, a trial of 17 444 patients undergoing orthopaedic surgery suggested an increase in myocardial infarction (MI) with aspirin at the dose of 160 mg per day. Many people randomized in primary prevention trials undoubtedly had undiagnosed ASCVD, but the

recommendations for prophylactic use of aspirin for primary prevention have been largely reversed, and the stage is set to reconsider the strength of evidence for giving aspirin for secondary prevention (9). Among patients with atrial fibrillation at high risk of bleeding, clinicians often prescribe aspirin instead of direct oral anticoagulants (DOACs) , despite its lower effectiveness for ischemic stroke prevention. In a systematic review and meta-analysis, DOAC therapy was not associated with a significantly higher risk of intracranial hemorrhage. These findings support the safety of DOAC compared with antiplatelet therapy (aspirin) and reinforce adherence to current atrial fibrillation guidelines (10).

Glucagone-like peptide 1-receptor agonists and the various outcomes

The effect of semaglutide on outcomes in knee osteoarthritis among persons with obesity has been studied in a 68-week, double-blind, randomized, placebo-controlled trial at 61 sites in 11 countries. Participants with obesity and clinical and radiologic diagnosis of moderate knee osteoarthritis with at least moderate pain were randomly assigned, in a 2:1 ratio, to receive once-weekly subcutaneous semaglutide (2.4 mg) or placebo, in addition to counselling on physical activity and a reduced-calorie diet. The primary endpoints were the percentage change in body weight and the change in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score (using a scale from 0 to 100, with higher scores reflecting worse outcomes) from baseline to week 68. A key confirmatory secondary endpoint was the physical-function score on the 36-Item Short Form Health Survey (SF-36), version 2 (using a scale from 0 to 100, with higher scores indicating greater well-being). A total of 407 participants were enrolled. The mean age was 56 years (81.6% of the participants were women), the mean BMI was 40.3 kg/m^2, and the mean WOMAC pain score was 70.9. The mean change in body weight from baseline to week 68 was -13.7% with semaglutide and -3.2% with placebo (P= <0.001). The mean change in the WOMAC pain score at week 68 was -41.7 points with semaglutide and -27.5 points with placebo (P= <0.001).

Participants in the semaglutide group had a greater improvement in SF-36 physical-function score than those in the placebo group (mean change, 12.0 points vs. 6.5 points; P= <0.001). The incidence of serious adverse events was similar in the two groups. Adverse events that led to permanent discontinuation of the trial regimen occurred in 6.7% of the participants in the semaglutide group and in 3.0% in the placebo group, with gastrointestinal disorders being the most common reason for discontinuation. Among participants with obesity and knee osteoarthritis with moderate-to-severe pain, treatment with once-weekly injectable semaglutide resulted in significantly greater reductions in body weight and pain related to knee osteoarthritis than placebo (11).

The SELECT is a randomised, double-blind, multicentre, placebo-controlled, event-driven phase 3 trial in 41 countries, carried out to investigate if semaglutide is beneficial in patients with atherosclerotic cardiovascular disease with a history of heart failure. A group of 17, 604 patients with a mean age of 61.6 years and a mean BMI of 33·4 kg/m^2 were randomly assigned to receive semaglutide or placebo. All patients had a history heart failure at enrollment. 2,273 (53.0%) out of 4,286 patients had heart failure with preserved ejection fraction, 1,347 (31.4%) had heart failure with reduced ejection fraction, and 666 (15.5%) had unclassified heart failure.

Patients with heart failure had a higher incidence of clinical events. Treatment with resulted in improved outcomes in both the heart failure with reduced ejection fraction and heart failure with preserved ejection fraction groups. Serious adverse events were less frequent with semaglutide versus placebo, regardless of heart failure subtype (12).

Also tirzepatide causes considerable weight loss, and its effects on cardiovascular outcomes were studied in an international, double-blind, randomized, placebo-controlled trial (731 patients with heart failure, and ejection fraction of at least 50%, and a body-mass index of at least 30 kg/m^2).

The two primary endpoints were a composite of adjudicated death from cardiovascular causes or a worsening heart failure event and the change from baseline to 52 weeks in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS). A total of 364 patients were assigned to the

tirzepatide group and 367 to the placebo group; the median duration of follow-up was 104 weeks. Adjudicated death from cardiovascular causes or a worsening heart-failure event occurred in 36 patients (9.9%) in the tirzepatide group and in 56 patients (15.3%) in the placebo group. Worsening heart-failure events occurred in 29 patients (8.0%) in the tirzepatide group and in 52 patients (14.2%) in the placebo group ,and adjudicated death from cardiovascular causes occurred in 8 patients (2.2%) and 5 patients (1.4%), respectively. At 52 weeks, the mean (±SD) change in the KCCQ-CSS was 19.5 ±1.2 in the tirzepatide group as compared with 12.7 ±1.3 in the placebo group (P= <0.001). Adverse events (mainly gastrointestinal) leading to discontinuation of the trial drug occurred in 23 patients (6.3%) in the tirzepatide group and in 5 patients (1.4%) in the placebo group.The Authors concluded that treatment with tirzepatide led to a lower risk of a composite of death from cardiovascular causes or worsening heart failure than placebo and improved health status in patients with heart failure with preserved ejection fraction and obesity (13).

Glucagon-like peptide-1 receptor agonists (GLP-1a), used to treat type 2 diabetes and obesity, may decrease alcohol consumption. A cohort study with a median follow-up time of more than 8 years indicates that individuals were at markedly lower risk of alcohol-related hospitalizations and hospitalizations due to somatic reasons when using GLP-1a, especially semaglutide, as compared with times they were not using them.

In summary, GLP-1a offer the promise to prevent the development of alcohol-related outcomes, but randomized clinical trials are needed to verify these preliminary findings (14).

Controversial Alzheimer's drug donanemab

A new investigation of FDA-approved Alzheimer's drug donanemab (Dnb) highlights concerns about excess deaths, missing safety data, and financial conflicts of interest among FDA advisory panel members who recommended approval.

Dnb is the latest in a new class of anti-amyloid drugs designed to target beta-amyloid, a protein believed to be a key factor of Alzheimer's disease (AD). The drug is facing scrutiny over its safety, effectiveness, and the process leading to its approval. An investigation has uncovered concerns about excess deaths (including deaths, brain haemorrhage, and oedema) among patients taking the drug, missing safety data, and extensive financial ties between drug manufacturers and the expert advisors who recommended its approval. Moreover, the investigation raised questions about Dnb effectiveness. Although the Dnb debate continues, it highlights the need for greater transparency and scrutiny in the drug approval process, particularly for treatments targeting complex diseases like Alzheimer's (15).

Long-term oxygen supplementation for at least 15 hours daily prolongs survival among patients with severe hypoxemia

Based on a nonrandomized comparison, long-term oxygen therapy has been recommended to be used for 24 hours per day, a more burdensome regimen. To test the hypothesis that long-term oxygen therapy used for 24 hours per day does not result in a lower risk of hospitalization or death at 1 year than therapy for 15 hours per day, a multicenter, registry-based, randomized, controlled trial involving patients who were starting oxygen therapy for chronic, severe hypoxemia at rest was conducted.

The patients were randomly assigned to receive long-term oxygen therapy for 24 or 15 hours per day. The primary outcome, assessed in a time-to-event analysis, was a composite of hospitalization or death from any cause within 1 year. Secondary outcomes included the individual components of the primary outcome assessed at 3 and 12 months. The risk of hospitalization or death within 1 year in the 24-hour group was not lower than that in the 15-hour group and the groups did not differ substantially in the incidence of hospitalization for any cause, death from any cause, or adverse events. Among patients with severe hypoxemia, long-term oxygen therapy used for 24 hours per day

did not result in a lower risk of hospitalization or death within 1 year than therapy for 15 hours per day.

In conclusion, these reports offer relevant information for improving patients' quality of life and reducing treatment costs (16).

Invasive treatment strategy for older frail patients with myocardial non STE infarction?

Whether a conservative strategy of medical therapy alone or a strategy of medical therapy plus invasive treatment is more beneficial in older adults with non-ST-segment elevation myocardial infarction (NSTEMI) is under discussion.

A prospective, multicenter, randomized trial involving patients, aged 75 years or older, with NSTEMI was supported by British Heart Foundation. The patients were assigned in a 1:1 ratio to a conservative strategy of the best available medical therapy or an invasive strategy of coronary angiography and revascularization plus the best available medical therapy. Patients who were frail or had a high burden of coexisting conditions were eligible. The primary outcome was a composite of death from cardiovascular causes (cardiovascular death) or nonfatal myocardial infarction assessed in a time-to-event analysis. A total of 1,518 patients underwent randomization; 753 were assigned to the invasive-strategy group and 765 to the conservative-strategy group. The mean age of the patients was 82 years, 45% were women, and 32% were frail. A primary-outcome event occurred in 193 patients (25.6%) in the invasive-strategy group and 201 patients (26.3%) in the conservative-strategy group (hazard ratio, 0.94; 95% confidence interval (CI: 0.77 to 1.14; P = 0.53) over a median follow-up of 4.1 years.

Cardiovascular death occurred in 15.8% of the patients in the invasive-strategy group and 14.2% of the patients in the conservative-strategy group (hazard ratio, 1.11; 95% CI: 0.86 to 1.44). Nonfatal myocardial infarction occurred in 11.7% in the invasive-strategy group and 15.0% in the conservative-strategy group (hazard ratio, 0.75; 95% CI; 0.57 to 0.99).

Procedural complications occurred in less than 1% of the patients. According to these data, in older adults with NSTEMI, an invasive strategy did not significantly lower the risk of cardiovascular death or nonfatal myocardial infarction than a conservative strategy over a median follow-up of 4.1 years. The results of this trial must be considered in the approach to older frail and multimorbid patients with NSTEMI (17).

Erectile dysfunction drugs don't mix well with nitrates after myocardial infarction (MI) or percutaneous coronary intervention (PCI)

A nationwide Swedish study bolsters the contraindication to using these drugs in combination. For men with a history of myocardial infarction or PCI, it may be risky to use nitrates for angina and phosphodiesterase-5 (PDE5) inhibitors for erectile dysfunction at the same time.

Compared with men taking nitrates alone, those who were also prescribed a PDE5 inhibitor had more significant risks of mortality and a range of adverse cardiovascular outcomes. That's contrary to what was hypothesized going into the study, and findings also are discordant with other recent studies suggesting that concomitant use of nitrates and PDE5 inhibitors does not raise the risk of cardiovascular events.

The growing number of patients who are using both types of agents, even though concomitant use is formally contraindicated due to the potential for relevant drops in blood pressure when they're combined, is driven by the desire for older men to maintain a high quality of life, including an active sexual life.

The contraindication to the combined use of nitrates and PDE5 inhibitors remains, even if it's critical to sort out the issue around the concomitant use of nitrates and PDE5 inhibitors because of the accumulating evidence suggesting that PDE5 inhibitors can be cardioprotective.

The first issue is educating primary care physicians. In that context, physicians must integrate the findings into what's known about the drugs' physiologic effects and how they interact with each other, taking into consideration that the general patient's quality of life is a critical part of treatment decisions (18, 19).

Transperineal versus transrectal prostate biopsy

A randomized multi-institutional clinical trial showed that a newer technique, called transperineal prostate biopsy (TPB) , reduced the risk of infection compared to traditional approaches.

The TPB collects prostate tissue via a needle through the skin of the perineum, in the area between the rectum and the scrotum. The procedure, which uses local anesthesia, allows physicians to bypass the traditional and more infection-prone route of collecting prostate biopsy tissue with a needle through the rectum.

The PReclude infection EVEnts with No prophylaxis Trans perineal (PREVENT) trial, funded by the

National Cancer Institute, found no infections among 382 men randomized to undergo the procedure compared with six infections affecting 1.6% of the 370 men randomized to undergo the traditional transrectal biopsy procedure. Transperineal biopsy should become the new standard of care for prostate biopsy: It was as effective as the transrectal biopsy approach to detect cancer without the risk of infection or the need for antibiotic prophylaxis (20).

Overtreatment of prostate cancer among men with limited life expectancy

Men with limited life expectancy (LE) have historically been overtreated for prostate cancer despite clear guideline recommendations. To determine if rates of overtreatment of men with limited LE have persisted in the active surveillance era and whether overtreatment varies by tumor risk or treatment, a cohort study was carried out in men with clinically localized prostate cancer in the Veterans Affairs health system, who received a diagnosis between January 1, 2000, and December 31, 2019.

LE was estimated using the validated age-adjusted prostate cancer comorbidity index (PCCI).

Treatment trends among men with limited LE were assessed using a stratified linear and log-linear Poisson regression in aggregate and across PCCI and tumor risk subgroups.The mean (± SD) age for the study population of 243,928 men was 66.8 (± 8.0) years. A total of 50, 045 (20.5%) and 11, 366 (4.7%) men had an LE of less than 10 years and LE of less than 5 years based on PCCI scores of 5 or greater and 10 or greater, respectively. Among men with an LE of less than 10 years, the proportion of men treated with definitive treatment (surgery or radiotherapy) for low-risk disease decreased from 37.4% to 14.7% (absolute change, -22.7%; 95% CI: -30.0% to -15.4%) but increased for intermediate-risk disease from 37.6% to 59.8% (22.1%; 95% CI: 14.8%-29.4%) from 2000 to 2019, with increases observed for favourable (32.8%-57.8%) unfavourable intermediate-risk disease (46.1%-65.2%).

Among men with an LE of less than 10 years who were receiving definitive therapy, the predominant treatment was radiotherapy (78%). Among men with an LE of less than 10 years, the use of radiotherapy increased from 31.3% to 44.9% (13.6%; 95% CI: 8.5%-18.7%) for intermediate-risk disease from 2000 to 2019, with increases observed for favourable and unfavourable intermediate-risk disease. Among men with an LE of less than 5 years, the proportion of men treated with definitive treatment for high-risk disease increased from 17.3% to 46.5% (29.3%; 95% CI: 21.9%-36.6%) from 2000 to 2019. Among men with an LE of less than 5 years receiving definitive therapy, the predominant treatment was radiotherapy (85%). The results of this cohort study suggest that, in the active surveillance era, overtreatment of men with limited LE and intermediate-risk and high-risk prostate cancer has increased, mainly with radiotherapy, despite clear guideline recommendations (21).

Tumors in older patients: new approaches?

Newer therapeutic strategies are also becoming of interest in geriatrics. In many hematologic malignancies, the adoptive transfer of chimeric antigen receptor (CAR T cells) has demonstrated notable success; nevertheless, further improvements are necessary to optimize treatment efficacy. Current CAR-T therapies are particularly discouraging for solid tumor treatment. The immunosuppressive

microenvironment of tumors affects CAR-T cells, limiting the treatment's effectiveness and safety. Therefore, enhancing CAR-T cell infiltration capacity and resolving the immunosuppressive responses within the tumor microenvironment could boost the anti-tumor effect (22). Specific strategies include structurally altering CAR-T cells combined with targeted therapy, radiotherapy, or chemotherapy. Overall, monitoring the tumor microenvironment and the status of CAR-T cells is beneficial and in further investigating the viability of such strategies and advancing CAR-T cell therapy, might get fair perspectives in older patients too.

Advancement in personalized regenerative medicine: integration with natural healing

There is an increasing need for more effective and accessible regenerative therapies that can enhance an older demographic's function and quality of life. The innovative approach leverages the body's inherent healing capabilities rather than attempting to recreate them artificially. Most of our body tissues have evolved to heal small ruptures or fractures with remarkable efficiency and reproducibility. The initial phases of this healing process are critical and rely on liquid blood forming the solid regenerative hematoma (RH), a rich living environment comprising key cells, macromolecules, and factors that trigger and regulate regeneration. For years, scientists have been looking at synthetic approaches to recreate the natural regenerative environment, which has proven difficult given its inherent complexity

A methodology that enhances, rather than replaces, the natural RH has been developed by combining synthetic peptide molecules with whole blood in animal models, suggesting broad potential applications in human regenerative medicine. The bio-cooperative approach could offer new possibilities for personalised treatments, as it utilises the patient's own blood to create bespoke regenerative materials.

The new methodology represents a departure from traditional tissue engineering and harnesses and enhances the body's existing regenerative mechanisms, potentially offering a more effective path to tissue repair. While the initial results are promising, particularly in bone repair. The ability to transform patient blood into tuneable regenerative implants could offer healthcare providers new options for personalised regenerative therapies., with a practical approach that could be implemented within clinical settings. Focus on working with rather than replacing natural healing processes could influence future developments in tissue engineering and regenerative medicine and provides proof-of-concept for a biocooperative approach that goes beyond biomimicry by using mechanisms that Nature has evolved to heal as tools to engineer accessible, personalized, and regenerative biomaterials that can be readily formed at point of use (23).

Conflict of Interest: The author declares that he has no commercial associations (e.g., consultancies, stock ownership, equity interests, patent/licensing arrangements, etc.) that might present a conflict of interest in connection with the submitted article.

References

1. Cucinotta D. Forever Young: mission impossible? Acta Biomed. 2024;95(6):e2024152. doi: 10.23750/abm.v95i6.16343.
2. Smith G. Diana. The New York Times. 2024 Dec 3.
3. Obsessed with the LifeSpan. Aging2.0. 2024 Dec 9. Available from: www.aging2.com.
4. Clocchiatti-Tuozzo S, Rivier CA, Renedo D, et al. Life's Essential 8 and Poor Brain Health Outcomes in Middle-Aged Adults. Neurology. 2024 Nov 26;103(10). doi: 10.1212/WNL.0000000000209990.
5. Glandorf L, Wittmann B, Droux J, et al. Bessel beam optical coherence microscopy enables multiscale assessment of cerebrovascular network morphology and function. Light Sci Appl. 2024;13:307. doi: 10.1038/s41377-024-01649-1.
6. Feron J, Segaert K, Rahman F, et al. Determinants of cerebral blood flow and arterial transit time in healthy older adults. Aging (Albany NY). 2024 Sep 18;16(18):12473-12497. doi: 10.18632/aging.206112.
7. Lin YC, Yan HT. Frailty phenotypes and their association with health consequences: a comparison of different measures. Aging Clin Exp Res. 2024;36:233. doi: 10.1007/s40520-024-02887-4.
8. Hioka A, Akazawa N, Okawa N, Nagahiro S. Influence of aging on extracellular water-to-total body water ratio in community-dwelling females. Clin Nutr ESPEN. 2024 Apr;60:73-78. doi: 10.1016/j.clnesp.2024.01.007.

9. Cleland JGF. Aspirin for Secondary Prevention of Atherosclerosis-Evidence or Dogma? JAMA Cardiol. 2024 Dec 4. doi: 10.1001/jamacardio.2024.4335.
10. Coyle M, Lynch A, Higgins M, et al. Risk of Intracranial Hemorrhage Associated With Direct Oral Anticoagulation vs Antiplatelet Therapy: A Systematic Review and Meta-Analysis. JAMA Netw Open. 2024 Dec 2;7(12):e2449017. doi: 10.1001/jamanetworkopen.2024.49017.
11. Bliddal H, Bays H, Czernichow S, et al. Once-Weekly Semaglutide in Persons with Obesity and Knee Osteoarthritis. N Engl J Med. 2024 Oct 31;391(17):1573-1583. doi: 10.1056/NEJMoa2403664.
12. Deanfield J, Verma S, Scirica BM, et al. Semaglutide and cardiovascular outcomes in patients with obesity and prevalent heart failure: a prespecified analysis of the SELECT trial. Lancet. 2024 Aug 24;404(10454):773-786. doi: 10.1016/S0140-6736(24)01498-3.
13. Packer M, Zile MR, Kramer CM, et al. Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity. N Engl J Med. 2024 Nov 16. doi: 10.1056/NEJMoa2410027.
14. Lähteenvuo M, Tiihonen J, Solismaa A, Tanskanen A, Mittendorfer-Rutz E, Taipale H. Repurposing Semaglutide and Liraglutide for Alcohol Use Disorder. JAMA Psychiatry. 2025 Jan 1;82(1):94-98. doi: 10.1001/jamapsychiatry.2024.3599.
15. Lenzer J, Brownlee S. Donanemab: Conflicts of interest found in FDA committee that approved new Alzheimer's drug. BMJ. 2024 Sep 25;386:q2010. doi: 10.1136/bmj.q2010.
16. Ekström M, Andersson A, Papadopoulos S, et al. Long-Term Oxygen Therapy for 24 or 15 Hours per Day in Severe Hypoxemia. N Engl J Med. 2024 Sep 19;391(11):977-988. doi: 10.1056/NEJMoa2402638.
17. Kunadian V, Mossop H, Shields C, et al. Invasive Treatment Strategy for Older Patients with Myocardial Infarction. N Engl J Med. 2024 Nov 7;391(18):1673-1684. doi: 10.1056/NEJMoa2407791.
18. Trolle Lagerros Y, Grotta A, Freyland S, Grannas D, Andersson DP. Risk of Death in Patients With Coronary Artery Disease Taking Nitrates and Phosphodiesterase-5 Inhibitors. J Am Coll Cardiol. 2024 Jan 23;83(3):417-426. doi: 10.1016/j.jacc.2023.10.041.
19. Levine GN. Erectile Dysfunction and Coronary Artery Disease: Unfortunate Bedfellows. J Am Coll Cardiol. 2024 Jan 23;83(3):427-429. doi: 10.1016/j.jacc.2023.10.042.
20. Hu JC, Assel M, Allaf ME, et al. Transperineal vs Transrectal Prostate Biopsy. The PREVENT Randomized Clinical Trial. JAMA Oncol. 2024;10(11):1590-1593. doi: 10.1001/jamaoncol.2024.4000.
21. Daskivich TJ, Luu M, Heard J, Thomas IC, Leppert JT. Overtreatment of Prostate Cancer Among Men With Limited Longevity in the Active Surveillance Era. JAMA Intern Med. 2025 Jan 1;185(1):28-36. doi: 10.1001/jamainternmed.2024.5994.
22. Xia X, Yang Z, Lu Q, et al. Reshaping the tumor immune microenvironment to improve CAR-T cell-based cancer immunotherapy. Mol Cancer. 2024;23:175. doi: 10.1186/s12943-024-02079-8.
23. Padilla-Lopategui S, Ligorio C, Bu W, et al. Biocooperative Regenerative Materials by Harnessing Blood-Clotting and Peptide Self-Assembly. Adv Mater. 2024 Dec;36(52):e2407156. doi: 10.1002/adma.202407156.

Correspondence:
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Domenico Cucinotta M.D.
Former Chairman of the Department of Internal Medicine and Aging,
University Hospital, Bologna
E-mail: cucin.d@libero.it