From Buonocore's Pioneering Acid-Etch Technique to Self-Adhering Restoratives. A Status Perspective of Rapidly Advancing Dental Adhesive Technology

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Summary: This literature-based OPINION PAPER reflects in an introductory historical perspective on the rapid advancement of dental adhesive technology. Past and current techniques to bond to tooth tissue, in particular to dentin as the most challenging bonding substrate, are critically appraised. Including the historical perspective in (1), this paper focuses on fourteen items thought to be of primary importance with regard to the current status of dental adhesive technology. In (2) the primary mechanisms involved in adhesion to enamel and especially dentin are dealt with having (3) also revisited the previously introduced adhesion-decalcification concept (AD concept) as basis of biomaterial-hard tissue interaction; the worldwide accepted classification of today's adhesives into etch&rinse (E&R) and self-etch (SE) adhesives are presented in (4), along with presentation of their respective PLUS-MINUS balances in (5) and (6); nomination of the GOLD-STANDARD E&R (7) and SE (8) adhesives is based on evidence of successful laboratory and long-term clinical performance, resulting in a recommended 3-step full E&R bonding route in (9) and the preferred 3-step combined selective enamel E&R with 2-SE bonding route in (10); (11) description of the main bond-degradation pathways and eight strategies to preserve bond stability; (12) coverage of the PROS and CONS of the newest generation of UNIVERSAL adhesives. Looking into the future, some expected future developments in dental adhesive technology have been suggested in (13), along with (14) a first status determination of the latest research-and-development towards self-adhesive restorative materials that no longer require any pre-treatment.

Keywords: review, bonding, dentin, adhesion, self-adhesive.

J Adhes Dent 2020; 22: 7–34.
doi: 10.3290/j.jad.a43994

Submitted for publication: 26.01.20; accepted for publication: 27.01.20

(1) HISTORICAL perspective of the MILESTONES in dental adhesive technology

Dental adhesive technology continues to evolve at a rapid pace (Fig 1). We have already learned to bond effectively and durably to enamel 65 years ago with Buonocore's invention of the "ACID-ETCH TECHNIQUE".[22] Predating Buonocore, the first attempts to bond acrylic resin to tooth structure should be attributed to the Swiss chemist Hagger in 1951.[63,110,111] He used the functional monomer glycerophosphate dimethacrylate (GPDM), which today is still contained as primary functional monomer in some popular dental adhesive products, such as the Optibond FL/XTR/Universal (Kerr) product family. Historical research identified Kramer and McLean, who showed in 1952 that GPDM improved adhesion to dentin by "penetrating the surface and forming an intermediate layer".[90] Much later, this inter-

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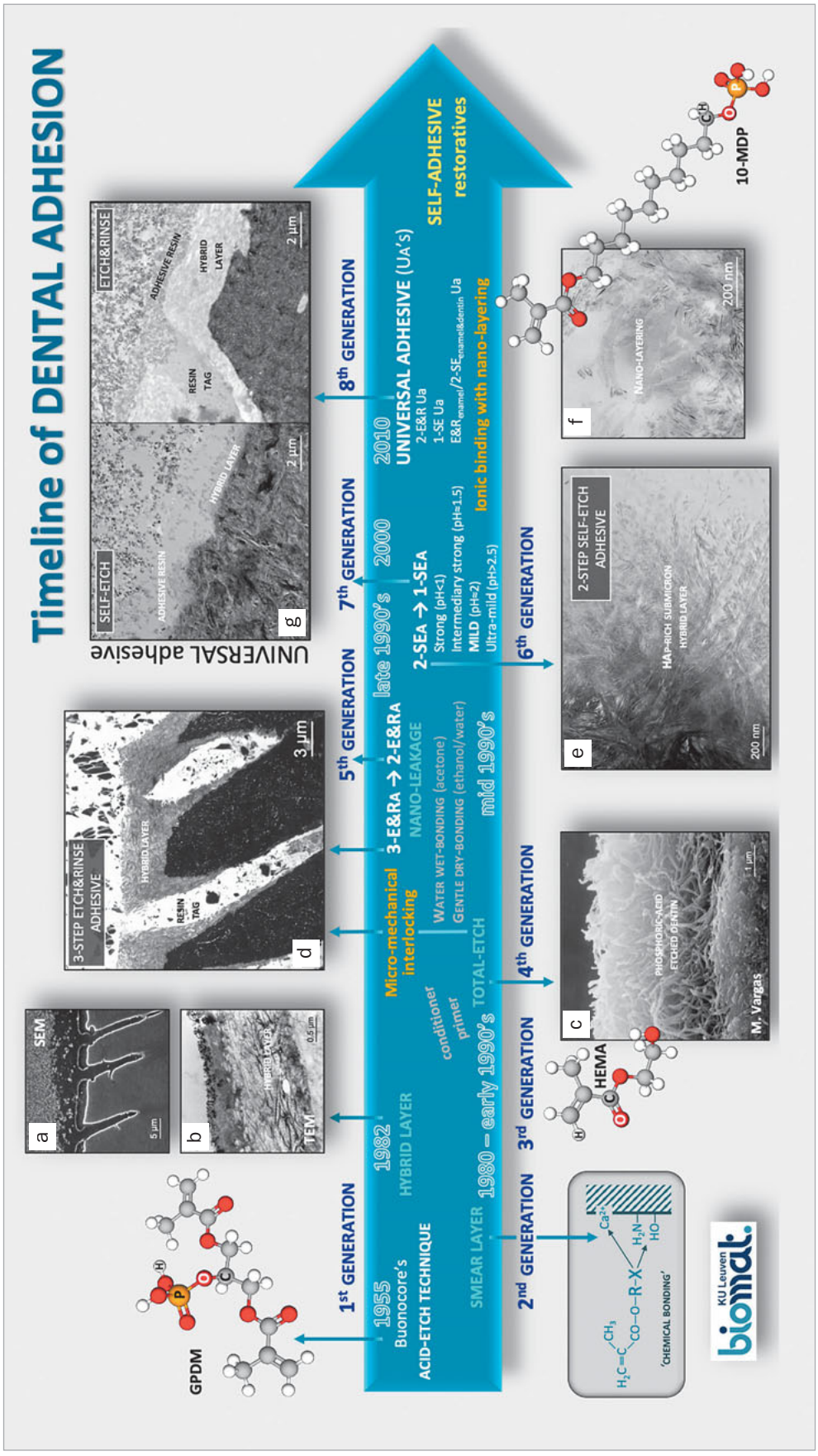

Fig 1 Schematic illustrating the historical evolution in dental adhesive technology.

mediate layer was labeled as the "hybrid layer".[126] However, history also learned that copying Buonocore's acid-etch technique to dentin, while generating 15-20 MPa bond strengths to enamel, was a logical but overly simple research-and-development (R&D) attempt.[21]

First-generation adhesives contained GPDM as active ingredient. GPDM has ionic bonding potential to hydroxyapatite (HAp) via its phosphate functional group (Fig 1). According to recent research, this chemical interaction of GPDM with HAp-based substrates should however be nuanced in the sense that although GPDM adsorbs onto HAp, it is incapable of forming a stable chemical bond.[244] Surface-active co-monomers like Bowen's N-(2-hydroxy-3-methacryloxypropyl)-N-phenylglycine (NPG-GMA) were added to the primitive GPDM-based adhesive formulations.[116] One of the first commercially available dentin bonding agents was commercialized as Cervident (SS White) in the 1960s.[16] These early adhesives, however, presented unstable, very low 2-3 MPa bond strengths to dentin.

In the late 1970s and the 1980s, research in dental adhesive technology focused on the synthesis of a wide range of functional monomers, all designed to chemically interact with either inorganic (HAp) or organic (collagen) dentinal components.[5,7,49,167] These **second-generation adhesives** were categorized into calcium- and collagen-bonding types.[6] Products like Clearfil Bond System F (Kuraray), which was already commercially available in 1978, Bondlite (Kerr/Sybron), J&J VLC Dentin Bonding Agent (Johnson & Johnson Dental) and Scotchbond (3M Dental) contained phosphorus esters of methacrylate derivatives. Some additional bond strength was gained, but it seldom exceeded 5-6 MPa, while these bonding agents were later also associated with suboptimal clinical outcomes.[71,197,223,231] These second-generation, mostly single-solution adhesives insufficiently dealt with the rather thick and compact SMEAR LAYER resulting from bur preparation. Surface smear was at that time insufficiently considered to interfere with potential (chemical) interaction of the functional monomer(s) with pure dentin substrate. These adhesives actually bonded to the smear layer, which in turn was too weakly attached to the underlying dentin. Typical of that time, "DENTIN BONDING AGENTS" were marketed, stressing their explicit design and development to bond to the challenging dentin substrate, while enamel bonding following acid etching was already considered satisfactory.

A milestone in the rapidly evolving dental adhesive technology was Nakabayashi's introduction in 1982 of the term "HYBRID LAYER" (Fig 1), which referred to the structure formed at the surface of dentin by prior (partial/full) demineralization followed by infiltration of monomers and their subsequent polymerization.[126] Abandoning the concept of chemical interaction with tooth tissue, as pursued with second-generation adhesives, the research community became gradually more convinced of the necessity to micromechanically interlock with tooth surfaces as a principal mechanism of adhesion. The basis for the **third-generation adhesives** was laid when the earlier Japanese concept of etching dentin to remove the smear layer, as already introduced by Fusayama et al in 1979,[57] gained worldwide acceptance and led to the commercialization of the Japanese bonding agent Clearfil New Bond (Kuraray) in 1984. Phosphoric-acid etching was followed by the application of a two-component chemically curing bonding agent that already contained the functional monomer 10-methacryloyloxydecyl dihydrogen phosphate (10-MDP). Today, 10-MDP is still considered one of the most effective functional monomers, but in bygone years was not used with the intention of chemically interacting with HAp. Following phosphoric-acid etching, no HAp remains up to a few micrometers depth at the dentin surface to interact with. Particularly in Europe and the United States, the application of phosphoric-acid etchants to dentin was then still discouraged because of their allegedly harmful effect on the underlying pulp, even with a dentin barrier in between.[13,164] Instead, smear-layer dissolution/removal was for instance obtained with a calcium chelator like EDTA (17%), which was applied and rinsed off prior to bonding using the well-known adhesive Gluma (Bayer Dental). Alternatively, aqueous acidic monomer solutions were used, such as the 'gold' bottle Scotchprep (3M Dental), which contained 2.5% maleic acid mixed with 55% 2-hydroxyethyl methacrylate (HEMA) as part of the popular two-step bonding agent Scotchbond 2 (3M Dental). As a third-generation adhesive, Scotchbond 2 (3M Dental) was one of the first bonding agents to receive the American Dental Association (ADA) label of "provisional acceptance" and later "full acceptance", which was based on successful short-term 1- and 3-year clinical results, respectively, recorded in independent clinical trials.[48,223]

To avoid pulpal collateral damage, milder phosphoric-acid alternatives, eg, maleic, nitric and citric acid, or lower concentrations of phosphoric-acid etchants were initially employed in gradual evolution towards **fourth-generation adhesives.** They make use of the "TOTAL-ETCH" technique, which was introduced based on Japanese research originally conducted by Fusayama's research group, who were much ahead of their time.[57,83] The term "total-etch" refers to simultaneous etching of enamel and dentin using phosphoric acid.[14,58] Along with research aims to interact with dentin more intensively, these total-etch adhesives evolved towards multi-step systems that included the separate use of a CONDITIONER and PRIMER prior to the application of the actual ADHESIVE RESIN in a typical three-step application procedure.[215] The term bonding agent no longer covered the multi-step application procedure and was therefore replaced by "ADHESIVE SYSTEM". While research understood that dentin, in contrast to enamel, required specific pre-treatment strategies, these multi-step adhesives presented more complicated and obviously more time-consuming clinical application procedures. The use of the term CONDITIONER originated in the early 1990s, which sounded less aggressive than etchant in traditional fear of adverse pulpal reactions. Besides complete smear-layer removal, 30-40% phosphoric-acid conditioning agents demineralize dentin up to several micrometers deep, and, upon thorough water rinsing, expose a microporous network of HAp-poor collagen fibrils (Fig 1c). The subsequently applied PRIMER

serves as an adhesion promoter. It contains hydrophilic monomers, such as the mono-functional monomer HEMA in particular. Thanks to its low molecular weight and thus small size, along with its high hydrophilicity through its short carbon chain ending in a hydroxyl group, HEMA is an effective surface-wetting as well as interdiffusion agent to infiltrate into the wet, demineralized collagen-rich dentin surface. Adequate infiltration should clinically be achieved within a short 10-20 s application time. Today, HEMA is still added to many commercial adhesives, also because it can act as co-solvent for other monomers in preventing water/monomer phase separation.[205,210] Major disadvantages of HEMA are, however, (1) its low polymerization ability, (2) low contribution to mechanical strength, (3) high water sorption and (4) its unfavorable biocompatibility, particularly in terms of its documented allergic potential.[208,209] In today's adhesives, manufacturers attempt to substantially reduce the HEMA content or even to replace HEMA with alternative monomers like methacrylamide monomer variants.

Typical total-etch primers contain monomers dissolved in different ethanol, acetone and/or water solvent combinations, with the solvent acting as carrier to facilitate monomer infiltration and resin envelopment of individual collagen fibrils. Upon application, the primer is gently air dried to promote solvent evaporation. If the solvent remained, it would harm hybridization and subsequent polymerization of resin within the 4- to 6-µm-thick hybrid layer. Hence, these total-etch primers primarily aim to make the moist collagen fibril network more receptive for subsequent infiltration of more hydrophobic monomers, as contained in the actual bonding agent or ADHESIVE RESIN applied in the third and final adhesive step. The infiltration of the latter into the open dentin tubules results in the formation of abundant resin tags, which along with intertubular hybridization constitute the primarily micromechanical interlocking bonding mechanism of total-etch adhesives (Figs 1a to 1d).

Along with the evolution of dental adhesive technology in the late 1980s and early 1990s, better understanding of the mechanisms involved in adhesion to dentin was gained by the introduction of new research techniques that enabled more profound characterization of adhesive-dentin interfaces at higher magnification/resolution. Especially noteworthy was the argon-ion bombardment technique developed by Inokoshi et al in the early 1990s, serving as a surface-topography enhancement technique to visualize hybrid-layer and resin-tag formation at adhesive-dentin interfaces using scanning electron microscopy (SEM) (Fig 1a).[80,179,220,221] Furthermore, Nakabayashi and Watanabe in 1983[127] and 1985[128] must have been among the first to report, initially in Japanese literature, on the use of transmission electron microscopy (TEM) to ultramorphologically characterize ultrathin 60- to 90-nm cross sections of adhesive-dentin interfaces.[129,130] TEM disclosed substantially more ultra-structural detail, basically enabling a look "inside" hybrid layers with artifact involvement minimized to section-shrinkage effects (Figs 1b, 1d to 1g).[184,185,186,188,196,213,216,217,226,227,230] While being much easier and therefore more frequently used, SEM interfacial characterization requires cross sectioning/polishing/fracturing techniques, by which the actual interfacial ultra-structure can never be observed free of artifacts; any defective resin infiltration will be obscured by specimen-preparation smearing effects.

The true breakthrough of the fourth-generation adhesives followed when worldwide etching of dentin with 30-40% phosphoric-acid etchants was no longer regarded harmful for the pulp. Even today, three-step adhesives are regarded as the first adhesive class reaching favorable clinical outcome.[39,42,148,152,222,223] A clear distinction needs to be made between total-etch adhesives that provide water/ethanol-based primers and those providing acetone-based primers. Vast scientific documentation on collagen-fibril collapse due to post-etching drying convinced most dentists to solely blot-dry dentin, keeping dentin visibly moist using the so-called (water) WET-BONDING TECHNIQUE.[61,62,84,85,185,186,188] Especially the bonding performance of adhesive systems that provide acetone-based primers benefited from wet bonding. Acetone helps to displace residual water, while water simultaneously keeps the demineralized collagen-fibril network accessible for resin infiltration. The greatest disadvantageous of the wet-bonding technique is, however, its high sensitivity to the correctly required degree of dentin-surface wetness, with both overwet and overdry dentin severely reducing adhesive performance.[147,184,186] Advantageously, adhesives providing water/ethanol-based primers appeared less sensitive to varying degrees of dentin-surface wetness.[226] A thirteen-year follow-up of class-V restorations bonded using Optibond FL (Kerr), a total-etch adhesive providing a water/ethanol-based primer, revealed a 94% retention rate when the adhesive was applied to gently air dried dentin and thus NO wet-bonding technique was applied.[150]

More recent classifications use the term 'ETCH&RINSE' (E&R) instead of total-etch, as today all adhesives are applied simultaneously to enamel and dentin. Classifying these adhesives as E&R adhesives clearly highlights the high clinical importance of the rinse phase and in particular the critical post-rinsing drying phase, in light of the above-mentioned dry/wet-bonding techniques.[215] The fourth-generation adhesives are today called three-step etch&rinse adhesives (3E&Ras), as they involve the successive application of a conditioner, primer and adhesive resin in three application steps (Fig 2).[215]

While dental adhesive technology evolved from one-step/component adhesives to three-step adhesives, having reached favorable long-term clinical effectiveness,[222,223] R&D focused in a next phase on SIMPLIFICATION, in the first place reducing the number of application steps (Fig 2), while commonly also claiming to reduce technique sensitivity of multi-step adhesives as a major marketing tool of the next generation(s) of simplified adhesives. Simplified adhesives combine at least two of the primary three etching, priming and bonding functions. However, they no longer allow application inaccuracies to be compensated by the next application step, so that they are arguably less forgiving of application errors. **Fifth-generation adhesives** are 2-STEP ETCH&RINSE ADHESIVES (2-E&Ras) that combine

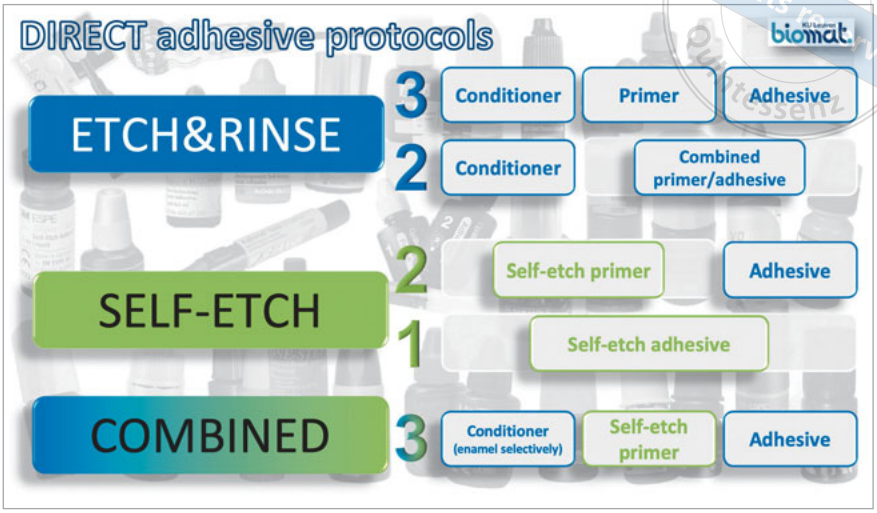

Fig 2 Overview of the direct adhesive protocols using conventional etch&rinse (E&R) and self-etch (SE) adhesives.

the primer and bonding agent in "one-bottle" adhesives (Figs 1 and 2).[215] While being popular in routine clinical practice, a significant price is paid for EASE-OF-USE, as 2-E&Ras generally present lower laboratory and clinical performance.[39,148,152] Their bonding performance typically improved when one-bottle adhesives were applied in multiple successive layers,[96] potentially separately light-cured, or were followed by the application of an extra bonding layer, basically transforming the simplified adhesives back into multi-step adhesives.[207] Other major shortcomings of 2-E&Ras, as compared to 3-E&Ras, are (1) their lower resin content along with higher solvent content,[209] (2) thinner adhesive film thickness with lower stress-absorbing effects,[46,118,142,225] (3) lower mechanical strength,[77,78] (4) higher hydrophilicity, permeability and water sorption,[68,103,163,183,193,195] and (5) generally reported lower laboratory bond-strength[39] as well as (6) inferior clinical performance, the latter particularly regarding class-V restorations and their annual failure rates.[148,152,215,222]

A major risk regarding bond stability associated with both 3- and 2-step E&Ras (previously known as total-etch adhesives) remains that dentin may be over-etched by phosphoric acid, deeper than resin will be able to infiltrate into the exposed collagen-fibril network in the short clinical application time. The phenomenon of 'NANOLEAKAGE', as introduced by Sano et al in 1995,[171,172] refers to the diffusion of small ions or molecules into incompletely resin-saturated hybrid layers in the absence of marginal gaps (which would cause microleakage). Such nanoleakage, also documented in 3D (Coutinho et al[36]), when associated with water sorption and hydrolysis, should be regarded as the principle BOND-DEGRADATION MECHANISM on dentin.[20,42,137]

Sixth-generation adhesives are today called 2-STEP SELF-ETCH ADHESIVES (2-SEas) that provide an acidic self-etch primer, basically combining the acid etchant with a primer, followed by the application of a classic adhesive resin (Figs 1 and 2).[215] Regarding application simplification, 2-SEas no longer require a rinse phase, so that they are sometimes also called 'etch&dry' adhesives (Lorenzo Breschi, personal communication). SE adhesives can be further subdivided according to their acidity and self-etch aggressiveness, as described below along with their simplified one-step versions.[215]

Seventh-generation adhesives are the true 1-STEP SELF-ETCH ADHESIVES or "all-in-one" adhesives that combine all three etching, priming and bonding functions in one single application step without a water rinse phase (Figs 1 and 2).[215]

Considering both 1- and 2-step SE adhesives together, self-etch adhesives can be further subdivided in 'STRONG' (pH<1), 'INTERMEDIARY STRONG' (pH=1-2), 'MILD' (pH≈2) and 'ULTRA-MILD' (pH>2.5) self-etch (SE) adhesives (Fig 1). One of the first marketed 1-step adhesives was Adper Prompt-L Pop (3M ESPE), which rapidly gained popularity among dental practitioners thanks to its easy and fast application in combination with a unique uni-dose packing/delivery system. However, unknown at the time of its introduction, the strong self-etch approach of Adper Prompt L-Pop (3M ESPE) as well as other strong SE adhesives led to instable bonding to dentin, while a relatively acceptable bonding performance to enamel was achieved thanks to their strong etching aggressiveness.[86,232] This 1-step adhesive contains methacrylic esters of phosphoric acid as functional monomers dissolved in water. Monomers such as diHEMA phosphate are not very stable in water; the adhesive even contained pure phosphoric acid, thus explaining its low acidity and strong (self-)etching performance. Similar to that produced by E&R adhesives, a thick 3- to 4-µm hybrid layer with full collagen exposure was produced at dentin with the difference that the dissolved calcium phosphates were not removed (rinsed off) but embedded within the hybrid layer. Strong SE adhesives failed on dentin as (1) collagen within the 3-4 µm was no longer supported by mineral, (2) no chemical bonding was involved, (3) the infiltrated resin did not adequately polymerize and remained highly hydrophilic,

Fig 3 Overview of the direct adhesive protocols using universal adhesives (UAs).

and (4) the calcium phosphates embedded in the relatively deeply exposed collagen-fibril network were not hydrolytically stable, which destabilized the adhesive interface with time. The documented accelerated bond degradation on dentin was later confirmed clinically in terms of higher restoration loss rates in the short term and higher annual failure rates compared to reference adhesives.[18,148,202]

The most favorable bonding performance to dentin was obtained with "MILD" SE adhesives that combine micromechanical interlocking with chemical bonding, of which their primary bonding mechanism is detailed below, since this class of (ultra)mild adhesives can today still be considered the most reliable approach to durable bonding to dentin (Figs 1e and 1f).[228,229] A major drawback, however, remains the inferior bonding effectiveness of mild and especially ultra-mild SE adhesives to enamel.[228] This should most likely be attributed to a combination of factors, ie, (1) the lower micromechanical interlocking potential achieved by the lower etching effect of the acidic functional monomers contained in (ultra)mild self-etch adhesives; (2) the lower chemical reactivity of functional monomers (also lower 10-MDP nanolayering; see below) with enamel HAp crystals; (3) which are larger with (4) a higher crystallinity than dentinal HAp crystals, making the targeted Ca more difficult to reach; and finally (5) also the parallel crystal organization in enamel rods as compared to the crisscross HAp orientation in dentin, making Ca easier to reach and interact with in dentin. Nevertheless, this drawback can clinically be compensated by selectively pre-etching enamel with phosphoric acid, then applying SE adhesive on the pre-etched enamel and unetched dentin. Along with the steadily growing use of mild SEas and – as enamel clearly requires phosphoric-acid etching and thus an E&R procedure – so-called SELECTIVE ENAMEL ETCHING, a clinically popular combined E&R/SE bonding routine has resulted (Fig 2).

Less common are "intermediary strong" SE adhesives that were developed as a compromise to bond more effectively to enamel through stronger etching, while not losing the chemical bonding potential to dentin. Two of the most successful adhesives in this class are the 1-SEa G-Bond (GC) that combines the functional monomers 10-DMP and 4-methacryloyloxyethyl trimellitic acid (4-MET),[23,122,155,201] and the GPDM-based 2-SEa Optibond XTR (Kerr), for both of which good laboratory and clinical data have been published.[44,52,75,151,200]

Mild 1-SEas evolved from combining the self-etch primer with the adhesive resin, which, as for the 2-step E&R adhesives, should generally be regarded as "TRADE-OFF" adhesives that are simple to use, at the expense of bond durability.[39,101,148,222] Nevertheless, the latest generation of 1-step adhesives has definitely improved in both laboratory and clinical performance, approaching the superior performance of multi-step adhesives.[228]

The newest eighth-generation adhesives are so-called UNIVERSAL ADHESIVES (UAs) that can be applied according to the dentist's personal choice in both full E&R or SE bonding modes, or the combined mode involving selective enamel E&R with a 1-SE bonding mode (Figs 1g and 3). These newest generation adhesives are extensively discussed further in this paper.

Today, bonding to dentin is still more challenging and has slowed down our adhesive endeavors for a long time. Nevertheless, adhesively restoring teeth in a RELIABLE, PREDICTABLE and DURABLE way can today be considered a fact.

One further simplification involves the development of SELF-ADHESIVE RESTORATIVE MATERIALS that no longer need separate pre-application of an adhesive.[218] They are the logical advancement of self-adhesive luting composites, obviously for restorative procedures requiring a higher level of self-adhesion. While the first self-adhesive restorative composites were released several years ago, their well-documented inferior performance both in laboratory and clinical research did not lead to a true breakthrough. However, it seems that a new era of self-adhesive restorative materials is just around the

corner, as new self-adhesive dental restoratives are being developed and marketed by different companies.

(2) PRIMARY MECHANISMS of adhesion

The primary adhesive mechanisms of any dental material intended to adhere to tooth tissue, particularly adhesives, cements and lately also self-adhesive restoratives, involve (1) SURFACE WETTING, (2) MICRORETENTION (or micromechanical interlocking) and (3) CHEMICAL INTERACTION (Fig 4). For durable bonding, one should clinically always strive to make optimal use of these three basic bonding mechanisms.

Adequate surface wetting is a primary requirement to achieve good interfacial contact between the adhesive material and the adherend or substrate. For a liquid to spread uniformly across a solid surface, the surface tension of the liquid must be less than the free surface energy of the substrate. Surface wetting behavior is commonly determined by contact angle measurements that ideally approach zero. Obviously, non-liquid materials, such as self-adhesive luting and restorative composites, have a certain viscosity that hampers their uniform surface spreading within a certain time period. Diverse factors play co-determining roles, such as (1) surface roughness, (2) substrates with high (eg, etched enamel) versus low (eg, smear-layer covered dentin) surface energy, (3) bond-promoting effects such as capillary forces (eg, bonding to etched enamel), (4) surface hydrophilicity/hydriphobocity, and (5) interfacial pores (air, moisture) that weaken the bond integrity. In complicated dental bonding to dentin as an intrinsically wet tissue (liquid-filled tubules), bondable materials should initially be hydrophilic (low water contact angle) to properly wet moist dentin, while ideally they should transform upon polymerization to a hydrophobic state (high water contact angle) to limit water sorption and prevent hydrolytic bond degradation.[42] Adhesives should hence achieve a balance between hydrophilicity prior to curing and hydrophobicity after polymerization. Hermetically sealing adhesive-dentin interfaces is principally impossible, considering the extremely high permeability of dentin with not only its numerous dentin tubules forming the direct connection to the pulp but also the highly microporous intertubular dentin structure. Bur debris directly interferes with surface wetting as it is smeared and compacted across enamel and dentin.[113,115,181,182,214] This surface smear should be adequately dealt with, as earlier bonding attempts clearly failed when they bonded to the smear layer, which was in turn insufficiently attached to the underlying unaffected tooth tissue. This smear layer should also be considered the major hurdle to be overcome by self-adhesive cements and restoratives that are applied without pretreatment and thus should sufficiently deal with this surface smear by virtue of their own chemistry.[114,119,156,180] Finishing cavities with smoother burs that leave thinner and less compact smear layers,[28,51] in addition to use of alternative cavity-preparation tools such as sono-abrasion, sand blasting and femtosecond laser ablation, are means of lowering smear-layer interference with bonding.[121,215]

Microretention or micromechanical interlocking is most likely the primary mechanism of bonding to mineralized tissues like enamel and dentin. Microretention can be achieved mainly in two ways, by MECHANICALLY (MICRO) ROUGHENING and by CHEMICALLY (SELF-)ETCHING. Cavity preparation by bur roughens the surface, by which surface contamination is removed. Furthermore, surfaces that are little receptive to bonding, such as aprismatic and fluorotic enamel, and glassy sclerotic dentin, need at least to be coarsened and optionally even partially/completely removed.[47,50,139,194,212,256] Self-evidently, surface debris is smeared across the cavity walls, which as mentioned above may interfere with bonding. Enamel unquestionably requires phosphoric-acid etching and sufficient microretention to achieve durable bonding.[137,215] Etching enamel removes any smear-layer interference; it simultaneously creates deep etched pits, in which relatively simple resins flow by capillary action and become micromechanically interlocked. Phosphoric-acid etching dentin has today become less preferred, as it completely demineralizes the 3- to 6-µm surface layer, exposing a microporous collagen-fibril network that hardly fully hybridizes through resin interdiffusion. Incomplete resin envelopment of exposed collagen makes the thick mineral-free and collagen-rich E&R hybrid layer less tight and less resistant to hydrolytic degradation and enzymatic biodegradation. Intense and durable chemical interaction of resin with collagen should not be expected with an E&R approach, as at best only secondary chemical bonding occurs, but generally will not contribute to bond durability. The alternative mild-SE approach makes use of acidic functional monomers that provide microretention to dentin by mild (self-)etching and thus partial demineralization of the 1-µm surface layer. They additionally rely on primary chemical (ionic) interaction of the functional monomer with HAp that remains abundantly available within the submicron hybrid layer (Figs 1e to 1g).

Indeed, chemical interaction is the most intimate contact possible between atoms and molecules and is thought to especially contribute to bond durability. It does not translate into higher bond strengths, but will prevent bond-strength reduction upon aging.[81] Chemical interaction should primarily target the inorganic HAp component of dentin with which to ionically interact, as part of the abovemen-

Fig 4 Basic bonding opportunities to bond to tooth tissue.

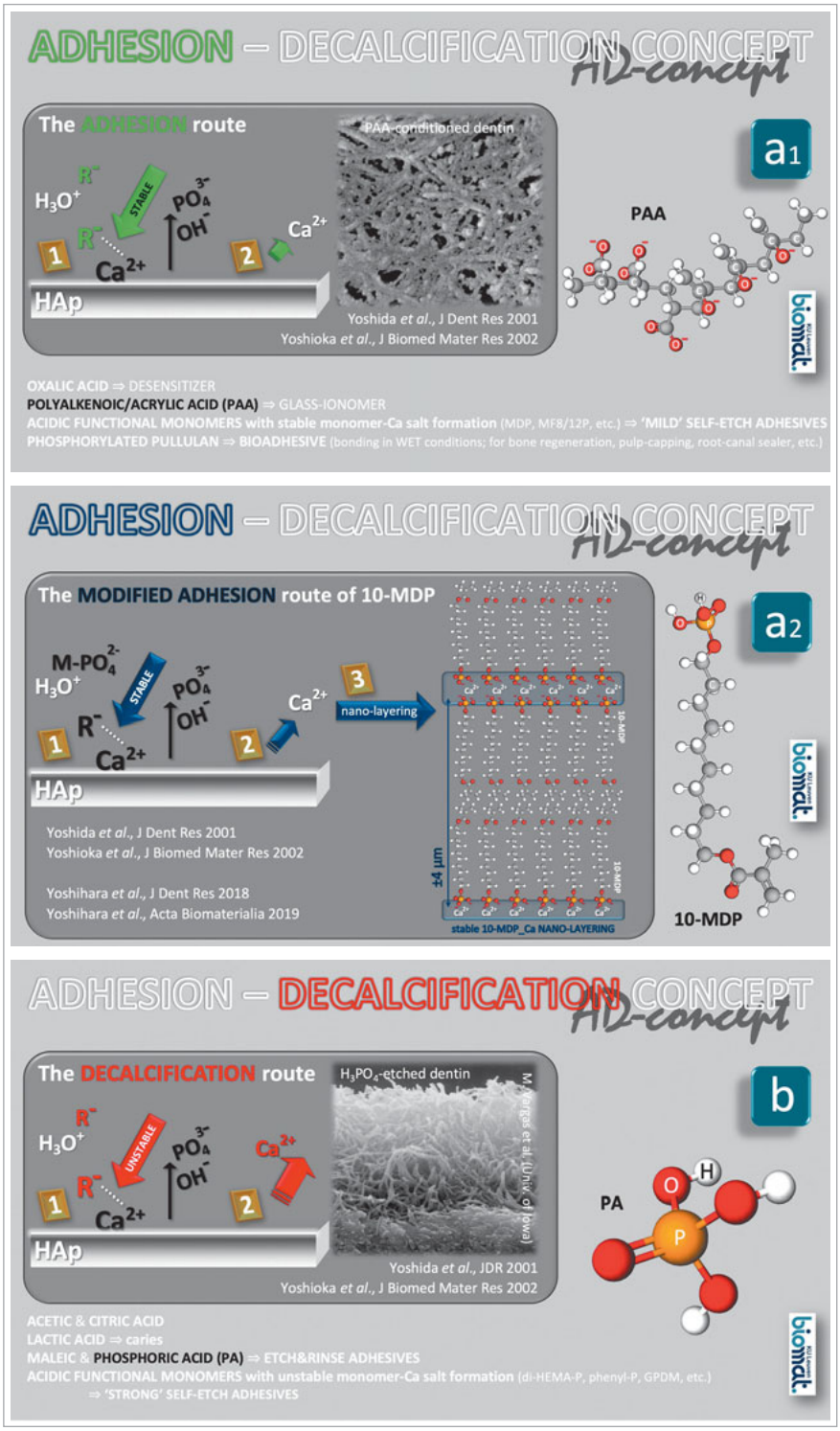

Fig 5 Schematic detailing the adhesion-decalcification (AD) concept with the ADHESION route in (a_1), the MODIFIED ADHESION route in (a_2), and the DECALCIFICATION route in (b).

tioned (ultra)mild SE bonding mode. Such primary chemical bonding with organic tissue components such as dentinal collagen is very challenging and usually only involves secondary weak van der Waals forces and hydrogen bonding that provide little degradation resistance.

(3) ADHESION-DECALCIFICATION concept revisited

Almost 20 years ago, the so-called AD concept was introduced by Yoshida et al in 2001[239] and Yoshioka et al.[255] This model is still valid today and defines how molecules interact with hard tissues like tooth enamel and dentin as well

as bone (Fig 5). It involves an adhesion (Figs $5a_1$,a_2) and decalcification route (Fig 5b). The key point is the formation of a stable ionic bond to calcium (Ca) within HAp or, in other words, the molecule's capacity to produce stable monomer-Ca salts. Determining the stability of monomer-Ca salts has been used to screen new candidate functional monomers for their chemical bonding potential.[211,237, 252,254]

Molecules like oxalic acid, polyalkenoic acid, specific acidic functional monomers and the more recently developed biodegradable phosphorylated pullulan (PPL) follow the ADHESION ROUTE, by which the molecules adhere to the HAp-based tissue with only a limited decalcification effect (Fig $5a_1$). Adhesion of the anion forces phosphate and hydroxyl anions to leave HAp to keep the interface electron neutral. The minor surface demineralization is beneficial in light of providing microretention (micromechanical interlocking). Oxalic acid, and oxalates in particular, have been used as dentin/root desensitizers,[27,189] as their simple, short molecular structure with two interconnected carboxyl groups stably ionically bonds to HAp's Ca; they form stable Ca salts that help to occlude open tubules as part of an effective treatment of dentin/root sensitivity. Polyalkenoic acids are polymers with abundant carboxyl groups that are able to "grab" (ionically bond to) Ca at so many different and adjacent HAp sites that they self-adhere to mineralized tissue.[56,238,239] Polyalkenoic acids are the functional polymers rendering conventional and resin-modified glass-ionomers self-adhesive to tooth enamel and dentin, while proper surface pre-conditioning with an aqueous polyalkenoic-acid conditioner remains necessary to reduce potential interference of bur smear with GI's self-adhesion.[37,43,82] As main functional ingredients, (ultra)mild SEas contain acidic functional monomers, of which the functional monomer 10-MDP (Fig 6) has been most extensively investigated for its chemical bonding potential. Such functional monomers ionically interact through their phosphate group with HAp's Ca,[237, 248,249,252] adding chemical bonding potential to the shallow microretention realized by the limited surface decalcification and etching effect induced by the acidic functional monomer. Finally, PPL has potential to bond in wet conditions, thus opening perspectives to be used as a "bioadhesive" for bone regeneration and pulp capping, and to serve as a functional ingredient of root-canal sealers.[29,140]

The unique chemical interaction of 10-MDP with HAp necessitated designing a MODIFIED ADHESION ROUTE (Fig $5a_2$). Among diverse acidic functional monomers, 10-MDP chemically (ionically) bonds to Ca of HAp but also etches and thus releases substantial Ca from the HAp-based substrate (Fig 6).[242] Such Ca release causes 10-MDP to self-assemble into about 4-nm nanolayers, a process driven by stable 10-MDP-Ca salt formation, a structure chemically first confirmed by Fukegawa et al in 2006[55] and later also visually proven using high-resolution TEM by Yoshihara et al in 2010.[252,254] Using scanning transmission electron microscopy (STEM), STEM energy-dispersive spectroscopy (EDS), x-ray diffraction (XRD) and nuclear molecular magnetic resonance (NMR), recent research ultra-morphologically and chemically characterized the mechanisms of interaction of

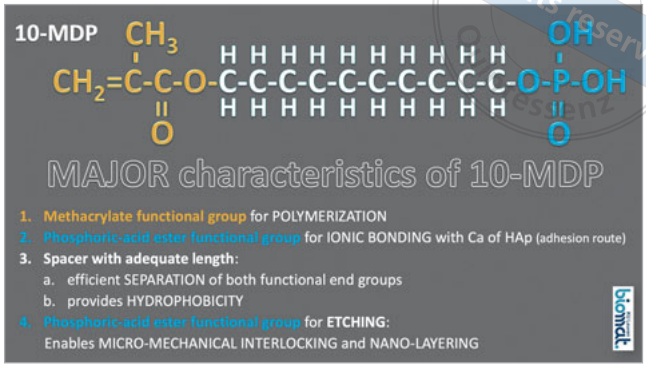

Fig 6 Major characteristics of today's most effective functional monomer 10-methacryloyloxydecyl dihydrogen phosphate (10-MDP).

10-MDP with bulk dentin in a manner similar to that which occurs clinically.[248] The hydrolytically stable 10-MDP-Ca salts were found to consist of $CaRPO_4$, meaning that the two hydroxyl (OH) groups of the phosphate group of 10-MDP ionically reacted with Ca. This stable structure is expected to contribute to durable nanolayering of 10-MDP-Ca salts in the hybrid and adhesive layer and hence improve clinical longevity of the adhesively bonded restoration.

When the ionic bond formed to HAp's Ca is not stable, a DECALCIFICATION ROUTE is followed (Fig 5b), as is done by acetic and citric acid, with the latter used as a root-canal irrigant in endodontics.[15,234] As Ca-lactate is not very stable, the continuous production of lactic acid by bacteria will result in progressive decalcification of tooth structure, which along with enzymatic MMP degradation of the dentinal matrix, will in the long term cause caries (cavities). As the Ca-salt of phosphoric acid is not very stable, this acid is an effective tooth etchant for an E&R bonding mode. Likewise, maleic acid has been used in the past as milder etchant replacing phosphoric acid. As mentioned above, one of the first 1-step adhesives, commercialized as Adper Prompt L-Pop (3M ESPE), was characterized as a "strong" SE adhesive, since the Ca salts of the contained functional monomer diHEMA-phosphate were not stable and easily dissociated into phosphoric acid; therefore, Adper Prompt L-Pop (3M ESPE) strongly etched enamel, rendering relatively stable adhesion to enamel, but it etched dentin too strongly, destabilizing its bond to dentin.

(4) CLASSIFICATION of today's adhesives

Dentin adhesion now implies using one of two approaches, namely the ETCH-AND-RINSE (E&R) or (ultra-)mild SELF-ETCH (SE) bonding mode.[215] Both bonding modes have their PROS and CONS in terms of bonding effectiveness and long-term bond durability, obviously with scientifically documented product dependency and a thoroughly documented better bonding performance of multi-step adhesives as compared to that of simplified TRADE-OFF E&R and SE adhesives.

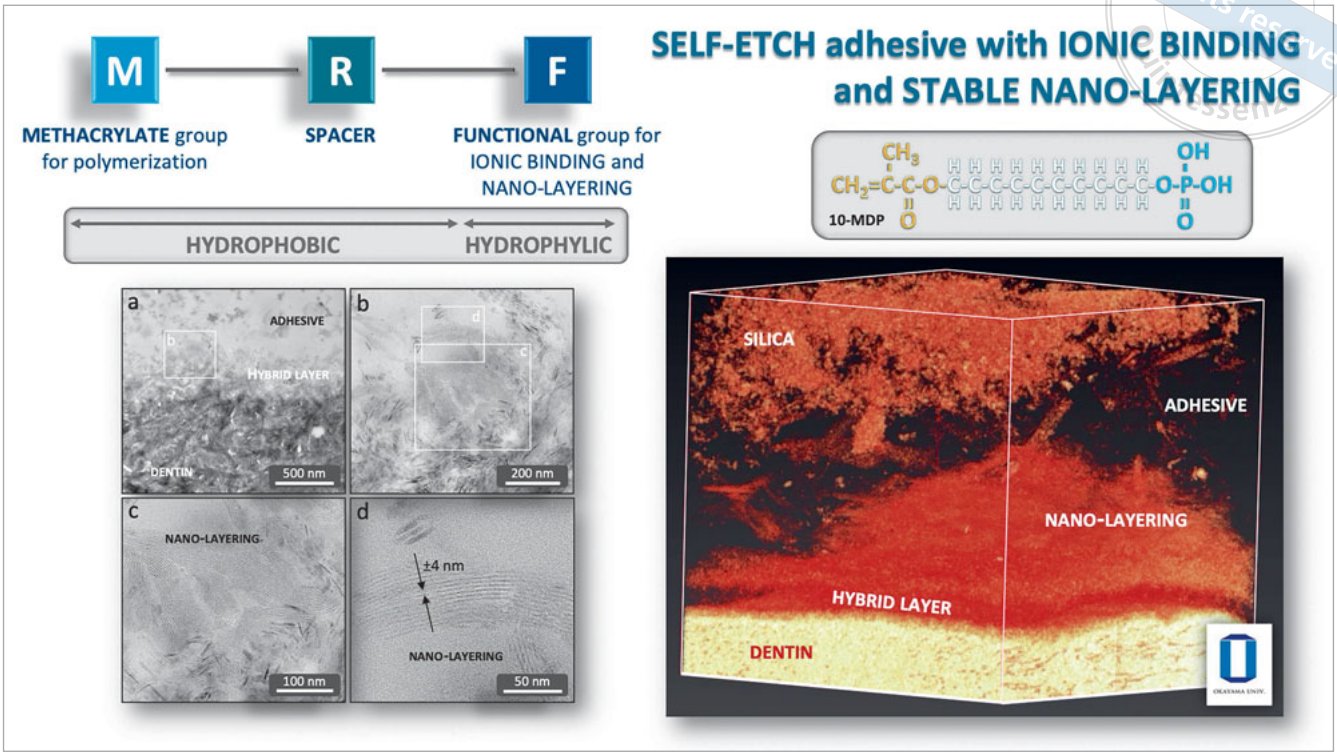

Fig 7 Bonding mechanism of a mild 10-MDP-based SE adhesive, explaining the primary ionic bonding of the (bi-)functional monomer 10-MDP with Ca of hydroxyapatite that remained within the submicron HAp-rich hybrid layer, along with stable 10-MDP-Ca nanolayering, as illustrated by transmission electron microscopy (TEM) photomicrographs of a representative adhesive-dentin interface at different magnifications in a-d, and the pseudo-3D focused ion beam/scanning electron microscopy (FIB/SEM) reconstruction of a similar adhesive-dentin interface.

The principal mechanism of E&R bonding can be described as diffusion-based micromechanical interlocking. The E&R technique involves phosphoric-acid etching to produce deeply etched pits in the HAp-rich enamel and to demineralize dentin up to a depth of 4 to 6 µm, exposing a HAp-free collagen network with an abrupt transition to the underlying unaffected dentin (Fig 1c). Any surface smear is completely removed. Upon rinsing off the phosphoric-acid etchant, enamel can be air dried, which turns it frosted white as a clinically visible sign that enamel was adequately etched. It is a disadvantage that this enamel-etch effect cannot be evaluated using a water wet-bonding technique, when the etched surface is solely blot dried and kept visibly moist. On enamel, phosphoric acid creates wide etched pits between the enamel prisms which, upon resin infiltration, result in MACRO-resin tags. At the enamel-prism cores, individual HAp crystals are thinned by (superficial) demineralization, while narrow but deeply etched pits are created, into which resin is drawn by capillary action to form MICRO-resin tags. Upon polymerization, resin is micromechanically interlocked, producing the most durable bond to tooth tissue, because of which enamel should always be preserved as much as possible when preparing teeth.

Bonding to dentin has always been more challenging. Following an E&R approach, phosphoric acid should be considered as rather aggressive on dentin, resulting in a time-dependent demineralization depth. Etching should definitely be limited to a maximum of 15 s in order not to over-etch dentin: the deeper dentin is etched, the more difficult it is for resin to infiltrate down to demineralization depth. Upon thorough water rinsing, a technique-sensitive water wet-bonding technique should mandatorily be applied for E&R adhesives that provide acetone-based primers (3-E&Ras) or combined E&R primer/adhesive resins (2-E&Ras). A gente dry-bonding technique is much less technique-sensitive for adhesives that provide water/ethanol-based primers (3-E&Ras) or combined primer/adhesive resins (2-E&Ras). Clinically, drying until etched enamel appears frosted white and dentin becomes dull, is easy to standardize. However, dentin should never be air dried too long (dried out), as collagen coagulates into clots that can hardly be infiltrated by resin. Upon gentle air drying, application of a water/ethanol-based primer will re-wet the partially collapsed collagen network, facilitating resin interdiffusion. The primer (or combined E&R primer/adhesive resin) should be applied at least for 15 s and actually cannot be applied long enough. Actively rubbing

the dentin surface with a microbrush using light finger pressure will locally intensify the functional monomer's interaction with dentin, basically "massaging" resin into the collagen network. Regularly applying fresh primer solution out of the dispensing well will further promote resin infiltration. The need to gently air dry the primed surface to help the primer solvent evaporate is often underestimated; in gentle air drying, the glossy film no longer moves as a clinical sign that primer solvent was adequately removed. Priming should be repeated/prolonged when dull spots remain discernable on the dentin surface. It is advantageous to have a primer containing a photo-initiator, in order to bring the photo-initiator deep into the exposed collagen network. The final step involves uniform application of the adhesive resin in a visibly thick layer that should always be separately and immediately light cured to stabilize the adhesive interface and block immediate water uptake through osmosis from the underlying dentin. Upon polymerization, resin is micromechanically interlocked by forming resin tags in dentin tubules as well as through inter- and intratubular hybridization without any primary chemical interaction involved.

Alternatively, (ultra)mild SE bonding simplifies dentin adhesion by bypassing the E&R process through incorporation of specific monomers with acidic functional groups, which concurrently behave as conditioning and priming agents. Self-etching enamel does not superficially dissolve and thin HAp as phosphoric acid does; it does not produce deep microretentive etching pits, by which the self-etching effect is insufficient to achieve durable bonding to enamel. Therefore, SE adhesives are commonly preceded by selective enamel etching with phosphoric acid following the clinical procedure described above.

The dentin surface is only partially demineralized upon (ultra)mild self-etching, by which microretention is only created within the first superficial micrometer and collagen remains surrounded and PROTECTED by HAp. Because surface smear may interfere with bonding, mild SEas are preferable to ultramild SEas. Prolonging self-etching will reduce smear layer interference. Upon resin infiltration, a typical submicron HAp-rich hybrid layer is produced, producing micromechanical interlocking with chemical bonding potential, as calcium remains abundantly available as a receptor to react with the functional monomer that infiltrated into this submicron hybrid layer. Of the many functional monomers investigated, 10-MDP is today the most effective (Fig 6). 10-MDP's major characteristics are: (1) its methacrylate functional group at one monomer end that enables the monomer to be incorporated within the 3D polymer network of the adhesive by copolymerization (Fig 6_1); (2) at the other end, 10-MDP possesses a hydrophilic phosphoric-acid ester functional group that can ionically bond to Ca of HAp (Fig 6_2) according to the adhesion route of the AD concept detailed above (Fig 5a). Among different functional monomers investigated, 10-MDP rates best for chemical bonding potential;[54,211,237,242,244,253] (3) the long carbon-spacer group effectively prevents steric hindrance between the methacrylate and phosphoric-acid ester group but also provides hydrophobicity to reduce water sorption (Fig 6_3), as well as enabling parallel self-alignment of adjacent 10-MDP molecules during nanolayering; (4) making 10-MDP unique among functional monomers is its substantial etching effect, producing microretention and thus enabling micromechanical interlocking, but also substantially releasing Ca from dentin as the driving force of 10-MDP nanola-ayering (Figs 6_4 and 7). While primary ionic bonding should be regarded as 10-MDP's major benefit, more data are currently being gathered, proving that nanolayering results in a stable 3D structures that additionally contribute to bond durability and thus merits further study. For instance, recent atomic-level chemical and ultramorphological structural analysis revealed that both hydroxyl groups of 10-MDP ionically react with Ca to produce a stable $CaRPO_4$ structure, which is resistant to water and acids.[248]

10-MDP is however not the perfect functional monomer, as it is still sensitive to hydrolytic degradation at its two esters linking both functional groups to the central spacer group (Fig 6). Indeed, 10-MDP appeared hydrolytically unstable in water, as it can degrade to hydroxydecyl dihydrogen phosphate and methacrylate.[2,124] Since SEas contain water, such monomer hydrolysis is expected to compromise their clinical performance.[123] Linking 10-MDP's favorable bonding potential to its molecular structure taught the research community how functional monomers with effective bonding potential to dentin should be designed, opening opportunities to synthesize 10-MDP analogues with similar bonding effectiveness but higher hydrolytic resistance. In this search for more hydrolytically stable functional monomers, phosphonate- and acrylamide-based monomers were synthesized, but have so far failed to approximate the bonding effectiveness and chemical interaction potential of 10-MDP.[124,252] However, the novel fluoro-carbon functional monomer 6-methacryloxy-2,2,3,3,4,4,5,5-octafluorohexyl dihydrogen phosphate appeared very promising, being referred to as MF8P and synthesized by Kuraray Noritake.[250] XRD and TEM revealed MF8P-Ca salt formation and nanolayering on dentin, as has been documented previously for 10-MDP.[249,252] The MF8P-Ca salt was as stable as that of 10-MDP, and MF8P was as hydrophobic as 10-MDP, while a significantly higher bond strength to dentin was recorded for MF8P than for 10-MDP.[250] This research concluded that despite its shorter molecular size, MF8P possesses characteristics similar to those of 10-MDP, most likely to be associated with the strong chemical bond between fluorine and carbon. Since favorable bond strength to dentin was recorded, MF8P can be considered a good candidate functional monomer for bonding. In continuation of the MF8P study, the longer-chain 12-carbon analog 8-methacryloyloxy-2,2,3,3,4,4,5,5,6,6,7,7-dodecafluorooctyl dihydrogen phosphate, referred to as MF12P, was found to be readily chemically adsorbed onto HAp and resulted in more stable bonding than 10-MDP and MF8P, confirming that MF12P is a good candidate functional monomer for durable bonding.[243] According to current knowledge, no commercial adhesives containing MF8/12P as functional monomer(s) currently exist, which most likely should be attributed to the higher monomer synthesis cost and thus the product price.

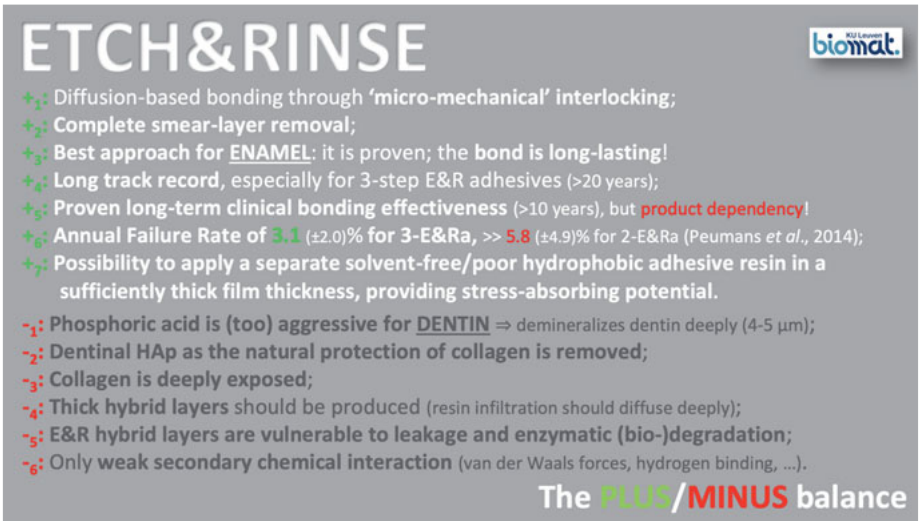

Fig 8 The PLUS-MINUS balance of conventional E&R adhesives.

(5) PLUS/MINUS BALANCE of ETCH&RINSE adhesives (Fig 8)

$+_1$: Most likely the major PLUS point of E&Ras is the effective diffusion-based bonding mechanism involving deep micromechanical interlocking both at enamel and dentin.[215]

$+_2$: Due to its etch aggressiveness, phosphoric acid completely dissolves surface smear that upon a thorough water spray is effectively removed, by which the smear layer will not interfere with bonding.

$+_3$: E&R is the best approach for enamel. It is proven; this bond to enamel is long-lasting.

$+_4$: E&Ras present with a long track record, especially for some 3-E&Ras that have been on the market for more than 20 years, such as the gold-standard 3-E&Ra Optibond FL (Kerr) (see below).

$+_5$: Independent evidence of long-term clinical bonding effectiveness of E&Ras in at least one randomized controlled clinical trial (RCT) beyond 10 years of clinical service exists in scientific literature, although a clear product dependency should be considered.[150]

$+_6$: According to a meta-analysis of clinical effectiveness in non-carious class-V lesions without macro-retention, the average annual failure rate (AFR) of 3-E&Ras was 3.1 (±2.0)%, which is significantly higher than that recorded for the more market-popular 2-E&Ras that presented with an average AFR of 5.8 (±4.9)%.[148] The latter AFR recorded for 2E&Ras also has a large(r) standard deviation, pointing to a relatively wide variance in clinical effectiveness recorded among commercial 2-E&Ras.

$+_7$: In particular, 3-E&Ras that involve the application of a separate resin-free/poor hydrophobic adhesive resin in a sufficiently thick film thickness, may provide shock/stress-absorbing potential in high-stress (polymerization shrinkage) cavity configurations. This emphasizes the need for sufficient film thickness, which current-generation UAs generally lack (see below).

$-_1$: MINUS is that phosphoric acid is (too) aggressive for dentin, by which dentin is deeply demineralized for 4-5 µm.

$-_2$: Dentinal HAp as the natural protection of collagen is completely removed/dissolved.

$-_3$: Collagen is deeply exposed (Fig 1c).

$-_4$: Thick hybrid layers should be produced in short clinical application times; resin should infiltrate several micrometers deep.

$-_5$: Thick E&R hybrid layers are vulnerable to micro/nanoleakage and enzymatic biodegradation.

$-_6$: Only weak secondary chemical interaction (van der Waals forces, hydrogen bonding) is involved, which will not substantially contribute to bond durability.

(6) PLUS/MINUS BALANCE of mild SELF-ETCH adhesives (Fig 9)

$+_1$: PLUS is the shallow hybridization of about 1 µm achieved with mild SEas, which is relatively easy for resin to diffuse in the short clinical application time. Not the hybrid-layer thickness but the hybrid-layer quality is of importance with regard to bond durability.

$+_2$: Dentin is only partially demineralized, sufficient to provide micromechanical interlocking.

$+_3$: Due to only partial demineralization, exposure of collagen is limited, so that it is better protected against enzymatic biodegradation.[40,41]

$+_4$: The submicron HAp-rich hybrid layer offers opportunities for primary chemical (ionic) interaction, although this depends highly on the functional monomer.[237,244,246,253] Today, 10-MDP is regarded as the most effective functional monomer that combines moderate etching,[242] providing surface microretention, with durable chemical interaction that additionally results in stable 10-MDP-Ca salt nanolayering.[241,248,249,251]

$+_5$: Mild SE adhesives also present with a long track record, especially for some 2-SEas that have been on the

Fig 9 The PLUS-MINUS balance of conventional mild SE adhesives.

market for more than 20 years, such as the SE gold-standard Clearfil SE Bond (Kuraray Noritake), with Clearfil SE Bond 2 (Kuraray Noritake) and its improved polymerization efficiency being the last version commercially available.

+6: Independent evidence of long-term clinical bonding effectiveness of SEas in at least one randomized clinical trial (RCT) beyond 10 years of clinical service exists in literature, although a clear product dependency should be considered.[149]

+7: According to a meta-analysis of clinical effectiveness in non-carious class-V lesions without macro-retention, the average annual failure rate (AFR) of 2-SEas was 2.5 (±1.5)%, with that recorded for the most easy-to-use 1-SEas (AFR = 3.6±4.9%) being only slightly lower than the AFR already mentioned above for 3-E&Ras (AFR = 3.1±2.0%).[148] As for 2-E&Ras (as compared to their 3-E&Ra counterparts), the AFR standard deviation of 1-SEas is substantially larger, again pointing to wide product variance.

+8: As advantageous for 3-E&Ras (compared to their 2-E&Ra counterparts), 2-SEas that involve the application of a separate resin-free/poor hydrophobic adhesive resin in a sufficiently thick film thickness, may provide shock/stress-absorbing potential in high-stress cavity configurations.

-1: MINUS is the unsatisfactory (self-)etching effect on enamel providing insufficient microretention for macro/micro-resin tag formation. As enamel requires phosphoric-acid and thus an E&R approach, selective enamel etching with phosphoric acid, reasonably avoiding etching of adjacent dentin, is recommendable and today a routinely applied technique.

-2: Potential smear-layer interference cannot totally be excluded, more interfering for ultra-mild (pH>2.5) than mild (pH≈2) SE adhesives.

-3: Although 10-MDP is today considered the most effective functional monomer (Fig 6) and therefore can be found in most SEas and even UAs (see below), 10-MDP is not perfect with regard to its hydrolytic stability.[124,170]

(7) GOLD-STANDARD E&R ADHESIVE (Fig 10)

When sufficient and consistent evidence of favorable long-term bonding performance appears from both laboratory and clinical research, commercial adhesives can be considered as GOLD STANDARD (GS).

GS1: Being on the market for more than 25 years, the 3-step E&R adhesive Optibond FL (Kerr) presented with the highest immediate and predicted 1-year bond strength to dentin in a meta-analysis including more than two thousand bond-strength tests reported in nearly 300 papers.[39]

GS2: As mentioned above, a high retention rate of 94% was recorded for Optibond FL (Kerr) in an independent thirteen-year RCT for non-retentive class-V restorations.[150] Noteworthy is that the 13-year clinical data were obtained when Optbond FL (Kerr) was applied following a gently dry-bonding approach. This significant finding emphasizes that as Optibond FL (Kerr) provides an ethanol/water-based primer, it can make use of self-rewetting effects to avoid collagen collapse that would prevent adequate resin infiltration, as has already been suggested a long time ago.[187,226] As definitely required for E&Ras that provide acetone-based primers (in case of 3-E&Ras) or combined primer/adhesive resins (2-E&Ras), the highly technique-sensitive water wet-bonding technique appeared redundant for Optibond FL (Kerr). Most likely also other E&Ras that provide water-based primers (3-E&Ras) or combined primer/adhesive resins (2-E&Ras) do not necessitate wet bonding. In other words, not all E&Ras need per definition be applied following the highly technique-sensitive wet-bonding technique, as many research reports and much commercial literature have seemed to suggest, even having sometimes led to wrongly calling E&Ras "wet-bonding" adhesives.

GS3: A very low AFR of 1.8 (±0.8)%, as based on 6 RCT's, was recorded for Optibond FL (Kerr) in a meta-analysis of clinical effectiveness of adhesives in non-retentive

Fig 10 Evidence justifying the nomination of OptiBond FL (Kerr) as gold-standard E&R adhesive, based on meta-analytical laboratory[39] and clinical data,[148] as well as on its superior clinical performance in a thirteen-year randomized clinical trial.[150]

Fig 11 Evidence justifying the nomination of Clearfil SE Bond (Kuraray Noritake) as gold-standard SE adhesive, based on meta-analytical laboratory[39] and clinical data,[148] as well as on its superior clinical performance in a thirteen-year randomized clinical trial,[150] though clinically recommended to be employed in a 3-step combined selective enamel E&R with 2-SE bonding mode.

class-V restorations,[148] the clinical model regarded as most suitable (most objective) to assess clinical effectiveness of adhesives.[222]

Based on two meta-analytic proofs of laboratory and clinical effectiveness along with one independent RCT, Optibond FL (Kerr) deserves to be recognized as gold-standard E&R adhesive (Fig 10).

(8) GOLD-STANDARD SE ADHESIVE (Fig 11)

GS1: Being on the market for more than 20 years, the 2-step SE adhesive Clearfil SE Bond (Kuraray Noritake; currently succeeded by Clearfil SE Bond 2 with claimed better polymerization efficiency) presented with the second highest mean immediate and predicted 1-year bond strength to dentin in a meta-analysis including more than 2000 bond-strength tests in nearly 300 papers.[39]

GS2: Currently, the 13-year retention rate of 96% recorded for Clearfil SE Bond (Kuraray Noritake) is the highest retention rate reported in independent long-term RCTs of non-retentive class-V restorations.[149]

GS3: A very low AFR of 2.2 (±1.7)%, as based on 12 RCTs, was recorded for Clearfil SE Bond (Kuraray Noritake) in a meta-analysis of clinical effectiveness of adhesives in non-retentive class-V restorations.[148]

Based on two meta-analytic proofs of laboratory and clinical effectiveness along with one independent RCT, Clearfil SE Bond (Kuraray Noritake) deserves to be recognized as gold-standard SE adhesive (Fig 11).

Having consistently produced favorable laboratory bonding-effectiveness data that have been confirmed by long-term clinical bonding-effectiveness data, it is hoped that both the gold-standard E&Ra Optibond FL (Kerr) and the gold-standard SEa Clearfil SE Bond 2 (Kuraray Noritake) are routinely used as control/references in laboratory research.

(9) RECOMMENDED full 3-step E&R bonding route

The recommended full E&R bonding route in three application steps is (Fig 12):

Etch enamel and dentin with 30–40% phosphoric acid, starting at enamel and finishing at dentin to limit dentin etching to 15 s maximum in order to not over-etch dentin. Water rinse briefly for 5–10 s and subsequently air dry until etched enamel appears white frosted as clinical sign of sufficient enamel etching and dentin appears dull. Dentin can only be shortly air dried, solely to visibly remove water. E&Ras that provide water-based primers are more technique forgiving and allow dentin to be gently air dried without compromising resin interdiffusion.

As the most important adhesive step, actively rub the primer onto both enamel and in particular dentin for at least 15 s. Priming cannot be done long enough: the longer, the better. Continuously apply "fresh" primer to the dentin substrate. Using a primer that also contains a photo-initiator is recommendable to bring the polymerization initiator deep into the exposed collagen-fibril network (while it will not cure at this step due to polymerization inhibition by oxygen). The priming step should be completed by gently air drying to promote solvent evaporation as much as possible.

Separately apply a solvent-poor/free adhesive resin in a visibly thick layer with stress-absorbing potential. After gently air-blowing to uniformly spread the adhesive resin (not to thin the adhesive's film thickness), the adhesive resin should ALWAYS be separately and immediately light-cured at dentin, also as part of indirect adhesive luting procedures using E&Ra-assisted composite cements but then after beforehand thorough air-thinning to avoid restoration-fit mismatches.[97,98] Immediate/separate adhesive polymerization will prevent rapid water sorption through osmosis from the underlying dentin.[190,208] Flowable composite is advised to be applied on top of adhesives that result in a thin film thickness to better stabilize the interface and enable the abovementioned stress-absorbing potential.

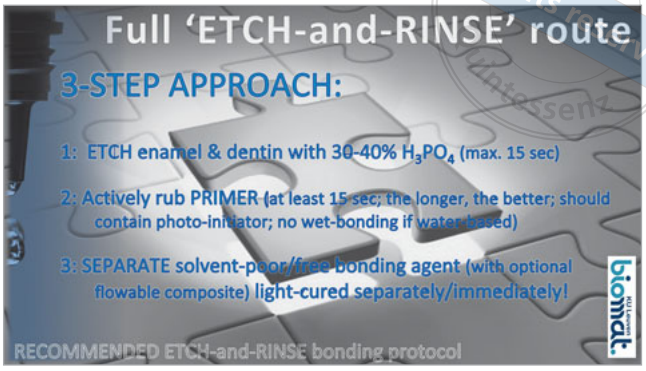

Fig 12 The recommended 3-step full E&R bonding route.

Fig 13 The preferred 3-step combined selective enamel E&R with 2-SE bonding route.

(10) PREFERRED 3-step combined selective enamel E&R and 2-SE bonding route

The preferred bonding protocol combines selective enamel E&R with 2-step SE in three application steps (Fig 13):

1. Selectively etch enamel with 30-40% phosphoric acid, avoiding etching adjacent dentin (although this should not be considered as very unfavorable, considering the reasonably good 3-E&R bonding mode mentioned above). If dentin is not touched, enamel etching can even be extended beyond 15 s. Thoroughly water rinse and air dry as described above for the recommended full 3-E&R route.
2. As the most important adhesive step, actively rub the 10-MDP-based mild self-etch primer for at least 15 s. Self-etch priming cannot be done long enough; continuously supply "fresh" primer onto the dentin substrate. Priming is ended with gentle air drying to promote solvent evaporation.
3. As for the full E&R route, apply in the final step a solvent-poor/free adhesive resin in a visibly thick layer with stress-absorbing potential. After gently air blowing to uniformly spread the adhesive resin, the adhesive resin should ALWAYS be separately and immediately light cured on dentin.

Considering being the most intimate contact achievable between atoms and molecules, chemical bonding should always be strived for to attain durable bonding to dentin. Therefore, the latter 3-step combined selective enamel E&R followed by 2-step SE bonding route should be considered as today's PREFERRED bonding protocol.

(11) Main BOND-DEGRADATION PATHWAYS and eight CLINICAL STRATEGIES proposed to PRESERVE BOND STABILITY

While modern dental adhesive technology has enabled durable bonding to enamel and dentin when proper bonding routines are clinically accurately followed, other NON-MATERIAL patient-, tooth- and/or operator-related circumstances may cause bonds to clinically deteriorate more rapidly.[45] In addition, laboratory research still reveals bond degradation upon accelerated aging regimes. Moreover, simplified bond-

ing protocols do not (yet) reach the bonding performance that can predictably be obtained using the abovementioned gold-standard adhesives and their recommended/preferred bonding routes. Several strategies have therefore been advanced to further optimize bonding and to counteract the main bond-degradation pathways, as there are (1) water sorption with hydrolytic bond-degradation mechanisms and (2) enzymatic bio-degradation, although the actual degree of involvement of the latter degradation pathway still remains unclear (see below). Eight strategies to potentially improve E&R and/or SE bonding have been proposed in recent literature (Fig 14).

1. Improving E&R and SE bonding by NON-THERMAL ATMOSPHERIC PLASMA treatment (for both E&Ras and SEas)

An interesting improvement in bonding following treatment of dentin with non-thermal atmospheric plasma (NTAP) has been suggested.[94] Plasma is defined as partially ionized gases that contain electronically excited atoms and molecules, as well as ionic and free-radical species. These highly reactive particles can crosslink rapidly to form various chemical functional groups on the surface of substrates. Overall, NTAP was suggested to affect different properties of relevance to dental bonding, such as increased dentin-surface wettability,[64] improved resin polymerization and deeper resin penetration.[64,94,258] Another possible reason for the bond-promotion effect might be that NTAP activates the dentin surface by depositing free radicals or peroxides, thereby intensifying the interaction between adhesive monomers and dentinal collagen.[32] Nevertheless, several laboratory experiments, using both microtensile bond strength and fracture-toughness testing, failed to provide consistent support in favor of dentin plasma treatment for improved E&R and SE bonding.[8,9,10] Thus, this strategy should not be considered sufficiently effective (Fig 14).

2. BIOMIMETIC REPAIR of E&R hybrid layers by REMINERALIZATION (for E&Ras)

A guided tissue-remineralization technique was introduced by Tay and Pashley in 2008.[192] Using this technology, proof-of-concept was achieved to biomimetically repair E&R hybrid layers.[95,191] This research aimed to develop a means of preventing degradation of denuded collagen within incompletely resin-infiltrated adhesive-dentin interfaces produced by E&R adhesives. A biomimetic remineralization scheme was shown to result in intra- and interfibrillar remineralization after several months.[17,87,191] While E&R hybrid layers could indeed be remineralized in the laboratory, the direct clinical applicability of this biomimetic strategy to extend the longevity of adhesive-dentin bonds is unclear. Moreover, the rationale behind the approach to first aggressively demineralize dentin using phosphoric acid as part of an E&R bonding mode, in order to use in a next phase a sophisticated (and long) protocol to remineralize the demineralized dentin surface, defies logic, especially considering that there exists an effective alternative SE approach, by which dentin is only partially demineralized and most dentinal collagen remains surrounded/protected by mineral. This dental remineralization technology may however be of interest to develop minimally invasive restorative techniques using materials with remineralization potential, for instance, so that no longer all carious tissue need be removed in deep caries lesions with a high risk of pulp exposure. Finally, the fact that E&R hybrid layers can be remineralized confirms how degradation-sensitive E&R hybrid layers really are, since fully resin-saturated E&R hybrid layers should not be remineralizable.

3. ETHANOL WET BONDING to improve resin-infiltration/interdiffusion (for E&Ras)

This strategy focuses on the E&R bonding mode with the intention to completely replace water within the exposed collagen-fibril network.[95] This strategy is based on a gradual exchange of surface water for ethanol, the latter solvent serving as a better medium to facilitate interdiffusion of in particular more hydrophobic resin into the by-phosphoric-acid deeply exposed collagen-fibril network.[137,138] This approach originated in specimen processing for electron microscopy, when after fixation specimens are gradually dehydrated in ascending ethanol concentrations prior to being critical-point dried or HMDS (hexamethyldisilazane) dried for SEM, or prior to being exchanged for epoxy resin and embedding in epoxy resin for TEM.[143,224] This method is most likely the most effective strategy to improve E&R bonding,[168,169] but is clinically impractical due to the clinical time needed for successive ethanol applications, as it requires at least several minutes (Fig 14).

4. INHIBITION of ENZYMATIC BIODEGRADATION (for E&Ras in particular)

Matrix metalloproteinases (MMPs) are a group of enzymes that are responsible for degradation of extracellular matrix proteins during organogenesis, growth and normal tissue turnover.[178] Although the expression and activity of MMPs in adult tissues has been reported to be normally quite low, MMPs, along with cysteine cathepsins, have been linked to biodegradation of adhesive-dentin interfaces.[95,109] Nevertheless, the proportional contribution of such enzymatic activity to bond degradation is still unclear. Hydrolytic effects due to water sorption most likely represent the most important/relevant bond-degradation pathway. Data regarding enzyme exposure and activation by the different kinds of adhesives are not always consistent, as well as the bond degradation-retarding/arresting effects upon use of MMP inhibitors vary among studies. It is very evident that MMPs are exposed/activated by phosphoric-acid etching following an E&R bonding mode, while this is not always confirmed for SE adhesives.[40,41] When for instance dentin powder was exposed to the gold-standard E&Ra Optibond FL (Kerr) and the gold-standard SEa Clearfil SE Bond (Kuraray Noritake) under clinical application conditions, gelatin zymography revealed the release of MMP-2 (not of MMP-9) by the E&R adhesive, while no release of enzymes could be detected for the mild SE adhesive, most likely due to the limited dentin-demineralization effect.[41] The latter contrasting data for E&R vs SE bonding were confirmed in a subse-

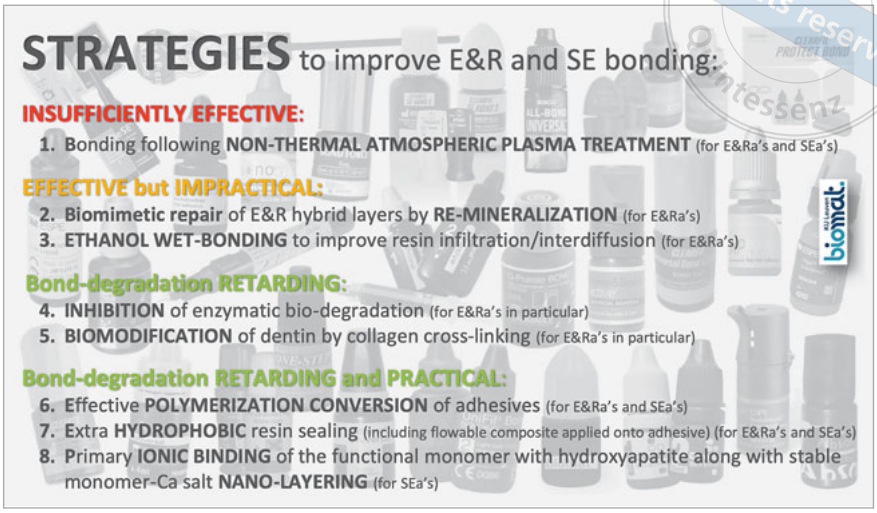

Fig 14 Critical appraisal of eight suggested strategies to improve E&R and SE bonding.

quent study on 2-E&Ra Scotchbond 1 XT (3M Oral Care), revealing MMP-2 presence (again no MMP-9), as opposed to the data recorded for the 2-SEa Clearfil Protect Bond (Kuraray Noritake) and 1-SEa G-Bond (GC), for which no enzyme activity was detectable.[40] Clearly depending on the adhesive's acidity and etching/demineralization aggressiveness, MMP activation was obtained by treating dentin powder with the strong SEa Adper Prompt L-Pop.[40] Although contradictory data have been reported in literature,[108] a significant direct correlation between gelatinolytic activity and the SE adhesive's pH was also found.[134] Overall, one may logically conclude that enzymes play a significantly larger role in bond degradation of E&R than SE adhesive interfaces, as was also recently confirmed by Li et al in 2019 (unpublished observations at KU Leuven BIOMAT).

To counteract enzymatic biodegradation, a long list of potential MMP inhibitors have been tested in laboratory research on their bond stability-promoting effect, as summarized in a systematic review and meta-analysis conducted by Montagner et al.[117] The MMP inhibitor documented most is the non-specific MMP-inhibitor chlorhexidine digluconate (CHX), which was (1) either incorporated into the acid-etching agent, which is rinsed away from the surface, (2) incorporated within the adhesive, or (3) applied as a solution directly on dentin after etching and so remains in contact with the surface (most often used MMP-inhibition strategy). A positive effect on maintaining bond stability was documented for relatively short-term specimen aging (up to 6 months), providing evidence that MMP inhibition can RETARD bond degradation. However, this effect was no longer detected for longer-term aging (1 year and beyond), by which one can state that MMP inhibition DOES NOT ARREST bond degradation (as hydrolytic bond degradation continues). In a representative study by Sadek et al,[168] 2% CHX was separately applied after phosphoric-acid etching. While a non-significant decrease in bond strength was obtained for the 3-E&Ra Scotchbond Multi-Purpose (3M Oral Care) and the 2-E&Ra Single Bond 2 (3M Oral Care) upon 9-month artificial aging, significant bond-strength reduction was recorded after 18-month aging despite the post-etching CHX treatment. However, when in the same study the two adhesives were applied following an ethanol wet-bonding technique, their bond strength remained stable after 9- and 18-month aging.[168] In full agreement with this study, bond strength to dentin of the gold-standard 3-E&Ra Optibond FL (Kerr) with CHX added to its primer did not significantly decrease with 3- and 6-month aging by specimen storage in water, while 12-month water storage resulted in a significant drop in bond strength down to the level of that when Optibond FL (Kerr) without CHX was applied.[41] Another study conducted by Zheng et al[259] revealed that four MMP inhibitors (2% CHX, 0.05% green tea extract, 1 mM ferrous sulfate, 0.2 mM galardin) prevented a decrease in bond strength of the gold-standard 3E&Ra Optibond FL (Kerr) upon 9-month aging but not of the gold-standard SE adhesive Clearfil SE Bond (Kuraray Noritake), for which the bond strength did not decrease with/without MMP inhibition. Searching for clinical evidence of bond-degradation inhibition, a meta-analysis conducted by Göstemeyer and Schwendicke,[60] though including only 10 RCTs and 7 studies that tested CHX, concluded that dentists can perform cavity pretreatments for inhibition of hybrid-layer degradation (they do not harm bonding), while a beneficial effect is (so far) not supported by sufficient clinical evidence.

In-situ zymography enabled precisely locating the proteolytic activity directly at the cross-sectioned adhesive interface.[107] When for instance 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) was used as an MMP inhibitor, the authors found that in situ zymography showed hybrid layers produced by the gold-standard 3-E&Ra Optibond FL (Kerr) and the market-representative 2-E&Ra Scotchbond 1XT (3M Oral Care) exhibited "intense" collagenolytic activity, while "almost no" fluorescence signal was detected when dentin was pre-treated with EDC.[107] Close evaluation of the pro-

vided in situ zymographic photomicrographs, however, disclosed a qualitatively significant difference in fluorescence, supposedly indicating collagenolytic activity, at the interfaces produced by the two adhesives investigated. Substantially more intense fluorescence was detected at the E&R hybrid layer (and within the underlying dentin tubules) produced by the 2-E&Ra; some reduction in fluorescence, though not very convincing due to the different angle of the 3D-reconstructed interfacial structure, appeared when dentin was pre-treated with EDC prior to adhesive application.[107] However, hardly any green fluorescence, indicative of collagenolytic activity, was observed at the 3-E&Ras interface; it even appeared to be concentrated at the top of the hybrid layer, where resin infiltration is expected to have occurred optimally, therefore potentially even having resulted in a false-positive result of in situ MMP activity. The limited collagenolytic activity located at an unexpected interfacial spot, along with total absence of green fluorescence after EDC pre-treatment, could have been more objectively interpreted as representing limited and totally absent collagenolytic activity, respectively, at the adhesive interface produced by an adhesive such as the gold-standard 3-E&Ra Optibond FL (Kerr), which has been abundantly documented to perform well. Hence, the sensitivity of the adhesive interface for enzymatic biodegradation seems adhesive/product dependent, and is clearly lower for those adhesives that have presented laboratory and clinical evidence of favorable bonding effectiveness.

Finally, recently unpublished research revealed that MMP-2 and -9 rapidly lose their activity (down to 35% of their initial activity within 24 hr and reaching nearly 0% after 1-week incubation on 37°C). Considering the limited lifetime of MMPs, one should question how MMPs are involved in the bond-degradation process, as they are solely activated by a one-time acidic adhesive treatment and in principle no further acidic activity occurs at the adhesive interface to expose/activate "fresh" MMPs. In contrast, in caries, enzymes are continuously produced in the acidic environment created by bacteria, and demineralization runs parallel with enzymatic degradation of the dentinal organic component, eventually leading to tooth decay (cavities).

5. Dentin BIOMODIFICATION by COLLAGEN CROSS-LINKING (for E&Ras in particular)

The working principle of this bond-promoting strategy involves besides inactivation of matrix-bound enzymes (MMPs), enhancement of intra- and intermolecular cross links of collagen, basically making collagen more resistant to biodegradation.[26] Both synthetic and naturally derived collagen cross linkers have been applied to bio-modify dentin, more specifically to make demineralized collagen-rich E&R hybrid layers more durable, with dentinal collagen fibrils possessing improved biochemical and biomechanical properties and higher resistance against enzymatic biodegradation.[105,106,136,175] The term "cross link" in biological sciences refers to the chemical bond between the side chains of amino acids within collagen molecules.[59] Intrinsic cross links stabilize the molecular arrangement within collagen fibrils, enhancing their tensile properties.[165]

Biomodification of dentin matrices by extrinsic collagen cross-linking has been proposed to enhance the fibrillar resistance against enzymatic degradation as well as to increase the tensile properties of the dentin matrix by the creation of additional inter- and intramolecular cross links.[11,53,70] Previous studies have demonstrated that various collagen cross-linkers, such as proanthocyanidin and glutaraldehyde in particular, indeed induce bond-promotion effects when employed in a wide range of application times (10 min – 40 h).[3,12,30,73,99] Some authors reported satisfactory results at clinically feasible times.[53,70,73,93,175] Convincing data in support of dentin-biomodification strategies have been reported, as for instance the use of three cross-linking primers, containing proanthocyanidin, riboflavin and glutaraldehyde, when applied for a clinically still relatively long time of 60 s prior to the application of the adhesive, appeared effective in minimizing bond-strength reduction of the 2-E&Ra Single Bond Plus (3M Oral Care) and the 1-SEa TetricN-Bond (Ivoclar Vivadent).[70] The stable bond strength assured with the two adhesives was attributed to reduced in-situ collagenolytic activity of MMPs, in particular when proanthocyanidin was used. As glutaraldehyde significantly reduced cell viability, it was correctly discouraged to clinically use it. However, less convincing data were obtained in a study conducted by Parise Gré et al.[136] While stable mini-interfacial fracture toughness was recorded after 6-month aging upon biomodification of dentin with 6.5wt% proanthocyanidin in a clinically relevant setting, the incorporation of UVA-activated 0.5 wt% riboflavin and 5 wt% glutaraldehyde in the dentin-bonding protocol appeared not to have been effective. Altogether, the benefit from using collagen cross linkers appeared in that study to be largely cross-linker and product dependent.[136]

6. Effective POLYMERIZATION CONVERSION of adhesives (for both E&Ras and SEas)

The importance of adequately polymerizing adhesives should not be underestimated. A well-polymerized adhesive layer is a basic prerequisite to achieve a long-term stable adhesive interface. As a general guideline, the adhesive should always be light cured separately and immediately upon its application onto dentin (and enamel). Doing so, water uptake of the adhesive interface from the underlying wet dentin through osmosis is reduced/blocked.[204,206,208,210] Often going against manufacturer's instructions, the adhesive should also be light cured prior to adhesively luting semi-direct/indirect restorations with E&R/SEa-assisted composite cements. While following a direct restorative procedure, the adhesive should best be applied in a visibly thick layer to achieve stress-absorbing potential, when adhesively luting semi-direct/indirect ceramic/composite restorations, the adhesive should be thoroughly air thinned until the adhesive no longer moves and does not pool prior to being light cured. In this way, perfect seating of the restoration is not compromised. Considering also that the adhesive luting procedure clinically takes a significant period of time, water droplets will be incorporated at the adhesive interface if the adhesive is not directly light cured.[97,98] Ob-

viously, such interfacial droplets/porosities weaken the adhesive interface and reduce the restoration's clinical lifetime. Laboratory research indeed showed that a complete auto-cure of adhesively luted ceramic restorations onto dentin, independent of the environment temperature that directly affects chemical curing (room vs body temperature), resulted in inferior immediate bond strength to dentin than when the adhesive (at the dentin side) was solely and separately light cured or when both the adhesive and composite cement were each separately light cured.[97,98] Pre-curing the adhesive prior to adhesive luting can safely be done without risk of restoration-fit complications, if the adhesive is before sufficiently air-thinned or modern UAs are employed that seldom reach a film thickness above 10 µm (depending also on air-blowing time/pressure). For good-fitting restorations, cement spaces are usually larger than 50 µm, by which solely a small part of the available space is consumed by the thinned and separately light-cured adhesive. Of course, when an "Immediate Dentin Sealing" (IDS) approach is employed prior to an adhesive luting procedure, the adhesive should not be air thinned and is best applied in a visible thick layer (eg, for direct restorations) followed by additional stabilization through application of a flowable composite on top of the adhesive layer.[157] There is then obviously no risk at all that the restoration cannot be perfectly seated, since the conventional/digital impression will be taken after the IDS procedure.

Bond degradation is directly related to water sorption.[95,160] The final adhesive interface should therefore be as hydrophobic as possible in order to limit water uptake. Adhesives should in the first place polymerize optimally,[19,25,69,132] considering in particular (1) their often hydrophilic nature, (2) the potential inclusion of residual solvent, and also (3) the thin film thickness of simplified single-solution adhesives and especially UAs (mostly below 10 µm) as opposed to polymerization inhibition by oxygen. To achieve long-lasting bonds, adhesives should be optimized to contain an effective photo-initiator system along with a monomer formulation that is well balanced for mono/bi-functional monomers as opposed to cross-linking monomers.[67,112] Besides measuring bonding effectiveness immediately and upon long-term aging, adhesives should be assessed for water solubility and water sorption in function of time, which should remain low at all times. In addition, their intrinsic mechanical properties (eg, ultimate tensile strength, fracture toughness) are to be determined in light of plasticization effects upon water uptake.[77,78,158]

In light of efficient polymerization of the adhesive, sufficient solvent removal from primers or combined primer/adhesive resin single-solution formulations, like UAs, is indispensable. Gently air-blowing upon their application until the resin film no longer moves is clinically recommended. The only exceptions are some HEMA-free and mostly acetone-based 1-step adhesives that should on the contrary be strongly air dried.[205] Within such adhesives, the adhesive monomers separate from water, a process triggered by rapid solvent evaporation once dispensed. Upon polymerization, the formed droplets will be entrapped within the adhesive, potentially jeopardizing bond durability. This can be avoided by strong air drying of the adhesive, thereby removing interfacial water and thus improving long-term bonding effectiveness.

7. Extra HYDROPHOBIC RESIN SEALING (for both E&Ras and SEas)

The placement of an extra bonding layer, resulting in (1) higher hydrophobicity, (2) better polymerization efficiency and (3) thicker film thickness, helps to stabilize and protect the adhesive interface more against water ingress from the underlying dentin tissue (through osmosis) as well as against water sorption from the outer oral environment. This clinically practical technique has repeatedly been advocated to improve the performance of in particular simplified 2-E&Ras and 1-SEas that combine the primer with the adhesive resin in a solvent-richer and resin-poorer single-solution adhesive, as likewise and more recently also for UAs that typically present with a thin film thickness. Both extensive laboratory[1,4,52,145,162,176] and clinical research[96,141] have demonstrated the bond-promotion effect of extra hydrophobic resin sealing, enabling the conclusion that the application of an extra hydrophobic layer will retard bond degradation of both E&R and SE bonding modes, basically by turning 2-E&Ras into 3-E&Ras, 1-SEas into 2-SEas and 1-SE/2-E&R_UAs into 2-SE/3-E&R_UAs. This strategy is indubitably clinically feasible and practical (Fig 14). Alternatively, a similar beneficial effect can be obtained by applying a flowable composite on top of a low film-thickness adhesive. This may be particularly beneficial in deep proximal boxes of posterior restorations, which additionally will lead to better marginal adaptation at the critical cervical and axial box margins;[166] the applied thicker flowable composite may then even serve as internal stress/shock absorber.[142,225,230] As mentioned above, flowable composite additionally applied onto the adhesive as part of an IDS procedure will also stabilize adhesive interfaces of adhesively luted semi-direct/indirect partial restorations.[100,157,199]

8. Primary IONIC BONDING of the functional monomer with HAp along with stable monomer-Ca salt NANOLAYERING (for SEas)

Mild self-etch and the newer UAs contain acidic (bi-)functional monomers.[146,228] Many different functional monomers have been synthesized and utilized in dental adhesives.[124,209] In general, such a functional monomer presents with a threefold molecular structure, consisting of an acidic functional group separated from a (metha)crylate group by a spacer group (Figs 6 and 7). The polymerizable (meth)acrylate group will co-polymerize with other monomers to be built in the resin matrix of the adhesive and adjacent resin-based composite. The spacer group, when sufficiently long, effectively separates the polymerizable (meth) acrylate group from the acidic functional group and provides hydrophobicity to the functional monomer. Potential acidic functional groups are phosphate, phosphonate or carboxyl groups,[124,209,228,242,244] which will either demineralize HAp or chemically bond to HAp, as defined by the adhesion-decalcification (AD) concept (Fig 5).[239,255]

According to this AD concept, acidic molecules adhere first to HAp by electrostatic interaction and either remain bonded through stable monomer-Ca salt formation following the ADHESION ROUTE (Fig 5a) or readily de-bond when no stable monomer-Ca salt is produced, resulting in abundant demineralization following the DECALCIFICATION ROUTE (Fig 5b). Previous studies demonstrated that the AD route followed by the functional monomer depends on its molecular structure with the acidic functional group inducing different etching abilities.[228,242] Following the decalcification route by strong SE adhesives (and E&R adhesives), a several micrometers deep hybrid layer is formed, in which substantial collagen is deprived from its surrounding HAp. The produced calcium phosphates are embedded within the exposed collagen fibril network, basically destabilizing the adhesive interface that becomes highly sensitive to hydrolytic degradation. This strong SE approach is no longer followed. Otherwise, the adhesion route will typically result in a submicron HAp-rich hybrid layer without much collagen exposure.

Besides the actual acidic functional group, the spacer group's chemical structure and its length co-determine the chemical interaction potential with HAp and dentin.[210,253] Among many functional monomers, 10-MDP is today considered one of the most effective monomers to strongly ionically bond to HAp, thereby forming stable 10-MDP-Ca salts (Figs $5a_2$, 6 and 7).[237,249] Moreover, 10-MDP was chemically and ultra-structurally demonstrated to self-assemble in nanolayers.[248,249,252,254] The chemically stable bond between 10-MDP and HAp was shown to contribute to bond durability, this evidenced by both laboratory[81] and clinical research,[148] with favorable long-term clinical data in particular having been recorded for the 10-MDP-based gold-standard 2-SEa Clearfil SE Bond (Kuraray Noritake).[149] The regularly structured monomer nanolayers are also thought to contribute to bond stability, with first direct evidence recently having been provided, as was detailed above.[248] Many of today's adhesives, and UAs in particular, contain the functional monomer 10-MDP, while more hydrolytically resistant 10-MDP analogues have already been synthesized,[243,250] but did not result in commercially available adhesives, most likely because of higher production costs and consequently higher market price.

(12) PROS and CONS of UNIVERSAL ADHESIVES (UAs)

Continued research in dental adhesive technology aims to improve the clinical techniques that dentists employ to adhere resin-based materials to tooth structure in light of a minimally invasive tooth-restoration concept.[31] The latest generation of UNIVERSAL ADHESIVES (UAs) combine the primer with the adhesive resin, enabling simplified and fast clinical bonding procedures with claimed relatively low technique sensitivity.[38,65,125,144,174] The term "UNIVERSAL" refers to their application options, enabling them to be used either following an E&R or SE bonding mode (Fig 3), while offering application versatility with (claimed) bonding potential to glass-rich (via silane) and glass-poor zirconia (via 10-MDP) ceramics for indirect tooth-restoration indications.[102,177,235,236,247]

The universal E&R bonding mode involves a phosphoric-acid etching step followed by a thorough water-rinsing phase prior to application of a primer/adhesive resin combination (Fig 3). Monomers diffuse into the created micro-etch pits at enamel to form micro- and macrotags and into the exposed collagen-fibril network at dentin to form a 3-5 µm hybrid layer, such as achieved by conventional E&Ras. This bonding mode thus makes primarily use of diffusion-based micromechanical interlocking. While the E&R bonding mode is undoubtedly the best bonding strategy to enamel, the resultant thick and HAp-free hybrid layer formed at dentin is highly sensitive to degradation with time (as detailed above for conventional E&Ras).

The universal SE bonding mode involves the use of monomers with an acidic functional (phosphate, carboxylate) group that in principle simultaneously etches (demineralizes) and infiltrates dentin up to about a 1-µm depth. In general, the SE bonding mode underperforms the E&R bonding mode on enamel, by which enamel remains to be selectively etched with phosphoric acid (E&R) (Fig 3). SE bonding nevertheless possesses chemical bonding potential as an additional benefit to achieve durable bonding. This chemical bonding capacity depends on the functional monomer contained. As mentioned above, 10-MDP is the most effective monomer today; it is uniquely bifunctional with a chemical bonding and polymerizing group at both monomer ends separated by a long hydrophobic spacer (Fig 6). As detailed above, 10-MDP (1) etches, thus releasing Ca from dentin, (2) ionically bonds to HAp's Ca, and (3) self-assembles into stable nanolayered Ca salts that spread three-dimensionally at the adhesive interface (Fig 7). 10-MDP's favorable bonding properties inspired most dental manufacturers to fabricate 10-MDP-based UAs.

In terms of immediate performance (restoration retention, marginal sealing), many currently commercially available adhesives are clinically effective, although some product-dependency exists. However, the long-term bonding performance of this new UA generation, in particular to dentin, is still insufficiently proven, and UAs have already also been associated with several shortcomings.[141] FIRST, their low film thickness, often below 10 µm, enables oxygen to inhibit polymerization of the adhesive layer for a significant fraction of its depth. Suboptimal polymerization insufficiently stabilizes the adhesive interface and may promote water sorption from the underlying dentin by osmosis. The thin adhesive layer is also thought to reduce the adhesive layer's ability to absorb stress (polymerization shrinkage) imposed onto the adhesive interface. SECOND, many UAs contain the mono-functional monomer HEMA. As mentioned before, being a small molecule with low molecular weight, HEMA is a good diffusing agent and additionally acts as a co-solvent for other less water-soluble monomers, especially because water is an essential (up to 40%) UA component to enable SE bonding potential. HEMA also helps to prevent phase separation between hydrophilic and hydrophobic adhesive components. However, HEMA's inherently high hydrophilicity also promotes water uptake through osmosis from the underlying dentin towards the adhesive in-

terface. HEMA does additionally not polymerize effectively and thus is only weakly built into the polymer network. Since HEMA makes the adhesive interface prone to hydrolytic degradation, alternative monomers for HEMA are definitely needed and are being incorporated in new UA formulations. A THIRD reason for potentially compromised bonding performance of UAs is related to the incorporated silane that many UAs contain to chemically bond to glass-rich ceramics, hereby avoiding the need for a separate ceramic (silane) primer.[235,236,247] These UAs cannot be very acidic (pH>2.5), so as to ensure silane's stability in the acidic aqueous solution; a higher pH however decreases UAs' etching and thus bonding efficacy. FOURTH and finally, although the functional monomer 10-MDP is effectively ionically bonds to HAp, resulting in stable monomer-Ca salt nanolayering,[240,248,249,251,252] 10-MDP's esters, linking the hydrophobic spacer to the methacrylate and phosphate functional groups at both monomers ends, are sensitive to hydrolytic degradation. This shortcoming encourages to search for 10-MDP analogues that combine superb chemical interaction with high hydrolytic resistance, as some 10-MDP analogues with improved hydrolytic stability have already been synthesized.[243,250]

UAs can optionally be applied in a full 2-E&R, a full 1-SE or a combined 2-step selective enamel E&R phase followed by a 1-SE bonding mode (Fig 3). Many UAs contain the today's most effective functional monomer 10-MDP. With a mainly diffusion-based micromechanical bonding mechanism, the function of 10-MDP is not entirely clear when UAs are used in an E&R mode. There have been some reports on chemical interaction of 10-MDP with collagen,[74] but this definitely requires further in-depth research to confirm the relevance of these findings with regard to the durability of the adhesive interface.

Although most UAs contain 10-MDP, differences in performance among 10-MDP-based UAs may still exist, as the 10-MDP concentration and quality (purity) have been shown to significantly affect bonding effectiveness.[228,246,254] Today, data on monomer concentration and quality are commonly not released by manufacturers and thus remain unknown.

(13) FUTURE DENTAL ADHESIVE TECHNOLOGY

It is not known if adhesives have reached a clinical performance level that can still be improved, in particular considering the documented superior performance of the gold-standard adhesives.[219] We do not know if we have reached a success rate well above 90% of what can be achieved with dental adhesion. To clinically distinguish adhesives in terms of bonding performance, a much longer follow-up is today needed to observe differences in clinical performance among the newest adhesive generations, even when compared to traditional gold-standard multi-step adhesives.[155] In addition, many current lecturers and papers stress that patient- and operator-related factors may have a higher impact on restoration longevity than the actual adhesive materials employed.[45] Nevertheless, further R&D remains needed to make adhesives less technique sensitive in conditions of suboptimal field control, to bond better/longer to low bonding-receptive tooth substrates, and eventually to develop economic, easy- and fast-to-place, self-adhesive "true" amalgam alternatives (see below).

In current research, the hype is to develop adhesive materials that do more than just bonding to tooth tissue. We all desire materials that have additional therapeutic potential, to be able to make our cavity preparations even less invasive than what is now possible with the current adhesive generation and to prevent early restoration replacement due to bond degradation and caries recurrence. Such a therapeutic effect is generally known as "BIOACTIVITY", although the definition is a matter of strong debate.[198] Bioactivity may potentially involve anti-bacterial, anti-enzymatic, and/or remineralization effects, all highly desirable material properties. Nevertheless, while it may not be that difficult to design and develop bioactive adhesive materials, combining bioactivity with mechanical stability may pose the greatest R&D challenge.

For instance, studies investigating materials containing bioactive glass filler have mainly focused on their bioactive efficacy. The results of laboratory research failed to show that surface pre-reacted glass-ionomer (sPRG) filled resin-based composites exhibited the desirable antibacterial properties, as the concentration of ions released by the restorative material did not appear sufficient to inhibit bacterial growth.[245] This study also showed that the sPRG-filled composite on the contrary promoted bacterial adhesion because of structural surface changes and increased surface roughness promoting biofilm attachment and formation. Although bioactive glass may exhibit antibacterial effects, this effect can be counteracted by an unstable surface integrity, which – upon ion release and in particular upon dissolution – results in rougher and more irregular restoration surfaces that promote bacterial adhesion. When aiming to develop bioactive materials that are clinically effective, it is essential not only to focus on their bioactive (antibacterial) characteristics but to make sure that the basic primary mechanical properties are maintained.

Furthermore, the clinical lifetime of adhesive restorations is still limited, as they remain more sensitive to (secondary) caries than unesthetic amalgam restorations.[89,120,135] Along with absence of anti-bacterial properties, lack of acid buffering may account for the higher susceptibility of composites to secondary caries.[133] To prevent secondary caries around composite restorations, adhesives and composites that contain anti-bacterial agents were developed.[33,35,257] For example, the anti-microbial monomer 12-methacryloyloxydodecylpyridiniumbromide (MDPB) was added to the commercial adhesive Clearfil SE Protect (Kuraray Noritake).[79,233] Many in vitro studies have confirmed the contact anti-bacterial effect of MDPB, while the clinical suppression of secondary caries by Clearfil SE Protect (Kuraray Noritake) has however so far not been proven (Clearfil SE Protect brochure, Kuraray Noritake). Besides quaternary ammonium methacrylate compounds immobilized into dental adhesives and composites without release potential, other anti-bacterial releasing agents like chlorhexidine and nanosilver particles have been investigated for their anti-caries properties, but they appeared less effective due to an uncontrolled, short-live burst release.[33]

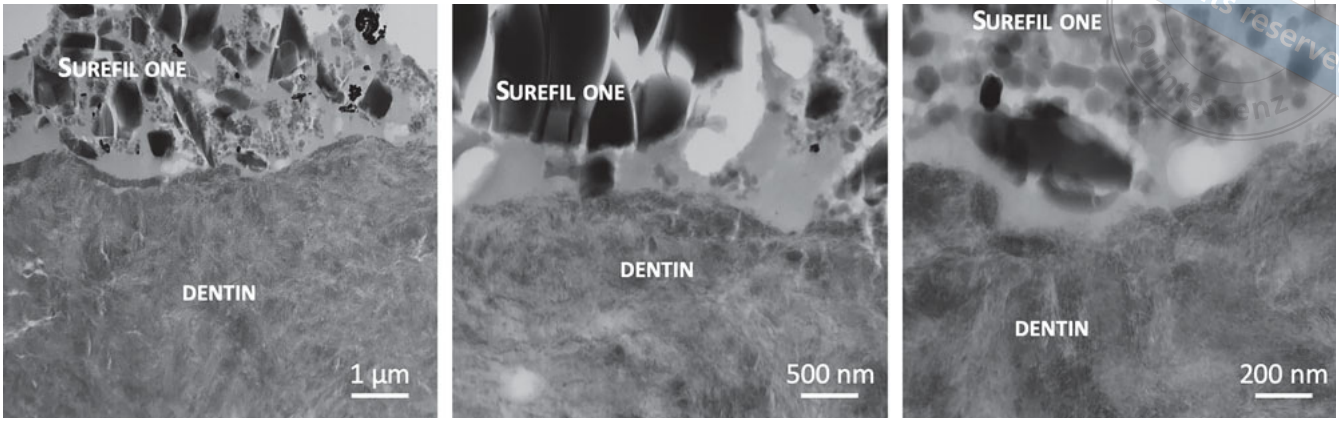

Fig 15 Transmission electron microscopy (TEM) of the interface produced by the self-adhesive bulk-fill restorative hybrid Surefil One (Dentsply Sirona) with bur-cut dentin. The self-adhesive restorative material tightly interacted with dentin, while no signs of surface demineralization or hybridization could be observed.

Cetylpyridinium chloride (CPC) is also a highly effective broad-spectrum anti-bacterial agent.[159] CPC disrupts the microbial cell membrane by disturbing its electric balance, a mechanism that is unlikely to be affected by micro-organism mutations and is pathogen independent.[131,159] A more in-depth description of CPC's anti-bacterial potential in the oral environment can be found in the literature.[24,76,92] FDA approved CPC as an over-the-counter drug and for use in oral hygiene aids, such as mouthwashes and toothpastes.[159] When CPC was incorporated into bonding resin in a previous study,[131] the anti-bacterial effect appeared to be confined to the area directly contacting the resin. To induce CPC release, CPC was incorporated in poly(2-hydroxyethyl methacrylate)/trimethylolpropane trimethacrylate hydrogels.[88] Such hydrogels could be recharged with CPC, but the CPC release remained relatively short; in addition, higher water sorption was reported as another drawback. To overcome this shortcoming, another promising strategy is to load CPC into an inorganic compound to release CPC in a controlled manner, as was studied before when CPC was incorporated into montmorillonite (Mont) clay,[34] referred to as 'CPC_Mont'. Besides CPC release, this CPC_Mont technology is considered to have CPC rechargeability. A recent study demonstrated that CPC can effectively be inserted into Mont and can also be re-charged with CPC.[104] Adding 1 or 3wt% CPC_Mont into a 1-step SEa conferred anti-bacterial properties to the adhesive without reducing the its bonding potential or increasing its cytotoxicity.[104]

(14) Ongoing evolution towards SELF-ADHESIVE RESTORATIVES

One further simplification involves the development of self-adhesive restorative materials that no longer need a separate pre-application of an adhesive. They are the logical advancement of self-adhesive luting composites,[72,153, 154,173] obviously for restorative procedures requiring a higher level of self-adhesiveness. While the first self-adhering restorative composites were marketed several years ago, their documented inferior performance, both in laboratory and clinical research,[114,156] did not lead to a true breakthrough. Self-adhesive flowable composites were first developed. According to the manufacturer's instructions, the first marketed self-adhesive flowable composite, Vertise Flow (Kerr), did not require any acid etching or bonding protocol prior to its application. Vertise Flow (Kerr) combines phosphoric-acid ester methacrylate with GPDM as functional monomers. Rahimian-Imam et al[161] reported that this self-adhesive flowable composite exhibited less microleakage than conventional fissure sealants. However, when used as a sealant in a split-mouth clinical trial, retention rates of the self-adhesive flowable composite were significantly lower compared to those of three conventional flowable composites bonded with an adhesive.[91] After 24 months, the retention rate of the self-adhesive composite was only 62.9%.[91] Another self-adhesive restorative material remained in an experimental phase and was not commercialized.[66] Nevertheless, the self-adhesiveness of this experimental restorative material to enamel and dentin was hypothetically ascribed to a form of nano-interaction, related to its relatively high pH (>2.0) and viscosity (as compared to conventional adhesive solutions).

New self-adhesive tooth restoratives are being developed and marketed by different companies, such as the so-called self-adhesive (bulk-fill) restorative hybrid Surefil One (Dentsply Sirona) (Fig 15).

When producing self-adhesive restoratives, some companies (first) target developing countries and position their new product in the dental market as an amalgam-replacement material, in part also in response to the global initiative of the United Nations Environment Program (UNEP) to reduce mercury consumption. Even though UNEP has questioned the environmental safety of amalgam, amalgam indeed remains the posterior restorative material of choice in many developing countries, where access to modern esthetic and more expensive dental composites is difficult.

Especially developed for these markets, such self-adhesive filling materials can nevertheless be a cost-efficient substitute for amalgam with a much better esthetic outcome. They are commonly instructed to be placed in bulk, like amalgam, without any additional adhesion-promoting means in retentive "amalgam" cavities, while a separate pre-etching step or adhesive application remains recommended to restore teeth that do not provide much macroretention. They are often powder-liquid formulations that claim to combine the simplicity of a glass-ionomer cement with the stability of conventional composite without sacrificing the esthetic outcome. When dentists can fill a cavity without an adhesive in just one bulk layer, the filling procedure will definitely be more efficient, in particular when such compromise materials are applied in less demanding cases when clinical time or financial aspects also have to be considered.

Other self-adhesive formulations claim additional bioactive properties, for instance, the product Activa Bioactive-Restorative (Pulpdent) included such a bioactive claim in its product name. According to the product specifications, this material is a "highly esthetic, bioactive composite that delivers all the advantages of glass ionomers in a strong, resilient resin matrix, while it chemically bonds to teeth, seals against microleakage, releases calcium, phosphate and fluoride, is more bioactive than glass ionomers, and is more durable and fracture resistant than composites". Originally, this product's instructions for use stated that it be applied in a nearly self-adhesive mode, only requiring brief etching in retentive cavities, while an adhesive has additionally been recommended in non-retentive cavities. However, a recently published randomized clinical trial investigating this material for posterior restorations when applied following the manufacturer's instructions was stopped already at one year due to an "unacceptable very high one-year failure frequency".[203] The authors concluded that further studies investigating this product should be conducted using a bonding agent; obviously, not only can the material no longer be considered self-adhesive, but also the claimed bioactive interaction with the surrounding tooth tissue is highly questionable as the material will no longer make direct contact with tooth tissue. Fortunately, the company adapted the material's instructions for use, now instructing not only to etch, but also to apply an adhesive of choice.

REFERENCES

1. Ahmed MH, De Munck J, Van Landuyt K, Peumans M, Yoshihara K, Van Meerbeek B. Do Universal Adhesives Benefit from an Extra Bonding Layer? J Adhes Dent 2019;21:117–132.
2. Aida M, Odaki M, Fujita K, Kitagawa T, Teshima I, Suzuki K, Nishiyama N. Degradation-stage effect of self-etching primer on dentin bond durability. J Dent Res 2009;88:443–448.
3. Al-Ammar A, Drummond JL, Bedran-Russo AK. The use of collagen cross-linking agents to enhance dentin bond strength. J Biomed Mater Res B Appl Biomater 2009;91:419–424.
4. Albuquerque M, Pegoraro M, Mattei G, Reis A, Loguercio AD. Effect of double-application or the application of a hydrophobic layer for improved efficacy of one-step self-etch systems in enamel and dentin. Oper Dent 2008;33:564–570.
5. Asmussen E, Bowen RL. Adhesion to dentin mediated by Gluma: effect of pretreatment with various amino acids. Scand J Dent Res 1987;95: 521–525.
6. Asmussen E, Munksgaard EC. Bonding of restorative resins to dentine: Status of dentine adhesives and impact on cavity design and filling techniques. Int Dent J 1988;38:97–104.
7. Asmussen E, Uno S. Adhesion of restorative resins to dentin: chemical and physicochemical aspects. Oper Dent 1992;Suppl 5:68–74.
8. Ayres AP, Bonvent JJ, Mogilevych B, Soares LES, Martin AA, Ambrosano GM, Nascimento FD, Van Meerbeek B, Giannini M. Effect of non-thermal atmospheric plasma on the dentin-surface topography and composition and on the bond strength of a universal adhesive. Eur J Oral Sci 2018a;126:53–65.
9. Ayres AP, Freitas PH, De Munck J, Vananroye A, Clasen C, Dias CDS, Giannini M, Van Meerbeek B. Benefits of Nonthermal Atmospheric Plasma Treatment on Dentin Adhesion. Oper Dent 2018b;43:E288–E99.
10. Ayres APA, Pongprueksa P, De Munck J, Gré CP, Nascimento FD, Giannini M, Van Meerbeek B. Mini-interfacial Fracture Toughness of a Multimode Adhesive Bonded to Plasma-treated Dentin. J Adhes Dent 2017;19:409–416.
11. Bedran-Russo AK, Pashley DH, Agee K, Drummond JL, Miescke KJ. Changes in stiffness of demineralized dentin following application of collagen crosslinkers. J Biomed Mater Res B Appl Biomater 2008;86: 330–334.
12. Bedran-Russo AK, Pereira PN, Duarte WR, Drummond JL, Yamauchi M. Application of crosslinkers to dentin collagen enhances the ultimate tensile strength. J Biomed Mater Res B Appl Biomater 2007;80:268–72.
13. Bertolotti RL. Conditioning of the dentin substrate. Oper Dent 1992; Suppl 5: 131–136.
14. Bertolotti RL. Total etch – the rational dentin bonding protocol. J Esthet Dent 1991;3:1–6.
15. Bohrer TC, Fontana PE, Lenzi TL, Soares FZM, Rocha RO. Can endodontic irrigating solutions influence the bond strength of adhesives to coronal dental substrates? A systematic review and meta-analysis of in vitro studies. J Adhes Dent 2018;20:481–494.
16. Bowen RL. Adhesive bonding of various materials to hard tooth tissues. II. Bonding to dentin promoted by a surface-active comonomer. J Dent Res 1965;44:895–902.
17. Brackett MG, Li N, Brackett WW, Sword RJ, Qi YP, Niu LN, Pucci CR, Dib A, Pashley DH, Tay FR. The critical barrier to progress in dentine bonding with the etch-and-rinse technique. J Dent 2011;39:238–248.
18. Brackett WW, Covey DA, St Germain HA Jr. One-year clinical performance of a self-etching adhesive in class V resin composites cured by two methods. Oper Dent 2002;27:218–222.
19. Breschi L, Cadenaro M, Antoniolli F, Sauro S, Biasotto M, Prati C, Tay FR, Di Lenarda R. Polymerization kinetics of dental adhesives cured with LED: correlation between extent of conversion and permeability. Dent Mater 2007;23:1066–1072.
20. Breschi L, Mazzoni A, Ruggeri A, Cadenaro M, Di Lenarda R, De Stefano Dorigo E. Dental adhesion review: aging and stability of the bonded interface. Dent Mater 2008;24:90–101.
21. Buonocore M, Wileman W, Brudevold F. A report on a resin composition capable of bonding to human dentin surfaces. J Dent Res 1956;35: 846–851.
22. Buonocore MG. A simple method of increasing the adhesion of acrylic filling materials to enamel surfaces. J Dent Res 1955;34:849–853.
23. Burrow MF, Tyas MJ. Clinical investigation of G-Bond resin-based adhesive to non-carious cervical lesions over five years. Aust Dent J 2012; 57:458–463.
24. Busscher HJ, White DJ, Atema-Smit J, Geertsema-Doornbusch G, de Vries J, van der Mei HC. Surfactive and antibacterial activity of cetylpyridinium chloride formulations in vitro and in vivo. J Clin Periodontol 2008;35:547–554.
25. Cadenaro M, Antoniolli F, Sauro S, Tay FR, Di Lenarda R, Prati C, Biasotto M, Contardo L, Breschi L. Degree of conversion and permeability of dental adhesives. Eur J Oral Sci 2005;113(6):525–530.
26. Cai J, Palamara JEA, Burrow MF. Effects of collagen crosslinkers on dentine: a literature review. Calcif Tissue Int 2018;102:265–279.
27. Camps J, About I, Van Meerbeek B, Franquin JC. Efficiency and cytotoxicity of resin-based desensitizing agents. Am J Dent 2002;15:300–304.
28. Cardoso MV, Coutinho E, Ermis RB, Poitevin A, Van Landuyt K, De Munck J, Carvalho RC, Van Meerbeek B. Influence of dentin cavity surface finishing on micro-tensile bond strength of adhesives. Dent Mater 2008;24:492–501.
29. Cardoso MV, de Rycker J, Chaudhari A, Coutinho E, Yoshida Y, Van Meerbeek B, Mesquita MF, da Silva WJ, Yoshihara K, Vandamme K, Duyck J. Titanium implant functionalization with phosphate-containing polymers may favour in vivo osseointegration. J Clin Periodontol 2017;44:950–960.

30. Castellan CS, Bedran-Russo AK, Karol S, Pereira PN. Long-term stability of dentin matrix following treatment with various natural collagen cross-linkers. J Mech Behav Biomed Mater 2011;4:1343–1350.
31. Chen C, Niu LN, Xie H, Zhang ZY, Zhou LQ, Jiao K, Chen JH, Pashley DH, Tay FR. Bonding of universal adhesives to dentine – Old wine in new bottles? J Dent 2015;43:525–536.
32. Chen M, Zhang Y, Dusevich V, Liu Y, Yu Q, Wang Y. Non-thermal atmospheric plasma brush induces HEMA grafting onto dentin collagen. Dent Mater 2014;30:1369–1377.
33. Cheng L, Zhang K, Zhang N, Melo MAS, Weir MD, Zhou XD, Bai XY, Reynolds MA, Xu HHK. Developing a new generation of antimicrobial and bioactive dental resins. J Dent Res 2017;96:855–863.
34. Chitrakar R, Makita Y, Hirotsu T, Sonoda A. Montmorillonite modified with hexadecylpyridinium chloride as highly efficient anion exchanger for perchlorate ion. Chem Eng J 2012;191:141–146.
35. Cocco AR, Rosa WL, Silva AF, Lund RG, Piva E. A systematic review about antibacterial monomers used in dental adhesive systems: current status and further prospects. Dent Mater 2015;31:1345–1362.
36. Coutinho E, Cardoso MV, Fernandes CP, Neves AA, Gouvea CV, Van Landuyt KL, De Munck J, Van Meerbeek B. Nanoleakage distribution at adhesive-dentin interfaces in 3D. J Dent Res 2011;90:1019–1025.
37. Coutinho E, Yoshida Y, Inoue S, Fukuda R, Snauwaert J, Nakayama Y, De Munck J, Lambrechts P, Suzuki K, Van Meerbeek B. Gel phase formation at resin-modified glass-ionomer/tooth interfaces. J Dent Res 2007;86:656–661.
38. Cuevas-Suárez CE, da Rosa WLO, Lund RG, da Silva AF, Piva E. Bonding performance of universal adhesives: An updated systematic review and meta-analysis. J Adhes Dent 2019;21:7–26.
39. De Munck J, Mine A, Poitevin A, Van Ende A, Cardoso MV, Van Landuyt KL, Peumans M, Van Meerbeek B. Meta-analytical review of parameters involved in dentin bonding. J Dent Res 2012;91:351–357.
40. De Munck J, Mine A, Van den Steen PE, Van Landuyt KL, Poitevin A, Opdenakker G, Van Meerbeek B. Enzymatic degradation of adhesive-dentin interfaces produced by mild self-etch adhesives. Eur J Oral Sci 2010;118:494–501.
41. De Munck J, Van den Steen PE, Mine A, Van Landuyt KL, Poitevin A, Opdenakker G, Van Meerbeek B. Inhibition of enzymatic degradation of adhesive-dentin interfaces. J Dent Res 2009;88:1101–1106.
42. De Munck J, Van Landuyt K, Peumans M, Poitevin A, Lambrechts P, Braem M, Van Meerbeek B. A critical review of the durability of adhesion to tooth tissue: methods and results. J Dent Res 2005;84:118–132.
43. De Munck J, Van Meerbeek B, Yoshida Y, Inoue S, Suzuki K, Lambrechts P. Four-year water degradation of a resin-modified glass-ionomer adhesive bonded to dentin. Eur J Oral Sci 2004;112:73–83. Erratum in: Eur J Oral Sci 2004;112(2):205.
44. Delbons FB, Perdigão J, Araujo E, Melo Freire CA, Caldas DD, Cardoso JL, Pagani M, Borges GA, Lima RB. Randomized clinical trial of four adhesion strategies in posterior restorations-18-month results. J Esthet Restor Dent 2015;27:107–117.
45. Demarco FF, Corrêa MB, Cenci MS, Moraes RR, Opdam NJ. Longevity of posterior composite restorations: not only a matter of materials. Dent Mater 2012;28:87–101.
46. Dietschi D, Monasevic M, Krejci I, Davidson C. Marginal and internal adaptation of class II restorations after immediate or delayed composite placement. J Dent 2002;30:259–269.
47. Duke ES, Lindemuth J. Variability of clinical dentin substrates. Am J Dent 1991;4:241–246.
48. Duke ES, Robbins JW, Snyder DS. Clinical evaluation of a dentinal adhesive system: three-year results. Quintessence Int 1991;22:889–95.
49. Erickson RL. Surface interactions of dentin adhesive materials. Oper Dent 1992;Suppl 5:81–94.
50. Ermis RB, De Munck J, Cardoso MV, Coutinho E, Van Landuyt KL, Poitevin A, Lambrechts P, Van Meerbeek B. Bonding to ground versus unground enamel in fluorosed teeth. Dent Mater 2007;23:1250–1255.
51. Ermis RB, De Munck J, Cardoso MV, Coutinho E, Van Landuyt KL, Poitevin A, Lambrechts P, Van Meerbeek B. Bond strength of self-etch adhesives to dentin prepared with three different diamond burs. Dent Mater 2008;24:978–985.
52. Ermis RB, Ugurlu M, Ahmed MH, Van Meerbeek B. Universal adhesives benefit from an extra hydrophobic adhesive layer when light cured beforehand. J Adhes Dent 2019;21:179–188.
53. Fang M, Liu R, Xiao Y, Li F, Wang D, Hou R, Chen J. Biomodification to dentin by a natural crosslinker improved the resin-dentin bonds. J Dent 2012;40:458–466.
54. Feitosa VP, Sauro S, Ogliari FA, Ogliari AO, Yoshihara K, Zanchi CH, Correr-Sobrinho L, Sinhoreti MA, Correr AB, Watson TF, Van Meerbeek B. Impact of hydrophilicity and length of spacer chains on the bonding of functional monomers. Dent Mater 2014;30(12):e317–323.
55. Fukegawa D, Hayakawa S, Yoshida Y, Suzuki K, Osaka A, Van Meerbeek B. Chemical interaction of phosphoric acid ester with hydroxyapatite. J Dent Res 2006;85:941–944.
56. Fukuda R, Yoshida Y, Nakayama Y, Okazaki M, Inoue S, Sano H, Suzuki K, Shintani H, Van Meerbeek B. Bonding efficacy of polyalkenoic acids to hydroxyapatite, enamel and dentin. Biomaterials 2003;24:1861–1867.
57. Fusayama T, Nakamura M, Kurosaki N, Iwaku M. Non-pressure adhesion of a new adhesive restorative resin. J Dent Res 1979;58:1364–1370.
58. Fusayama T. Total etch technique and cavity isolation. J Esthet Dent 1992;4:105–109.
59. Goh KL, Meakin JR, Aspden RM, Hukins DW. Stress transfer in collagen fibrils reinforcing connective tissues: effects of collagen fibril slenderness and relative stiffness. J Theor Biol 2007;245:305–311.
60. Göstemeyer G, Schwendicke F. Inhibition of hybrid layer degradation by cavity pretreatment: Meta- and trial sequential analysis. J Dent 2016; 49:14–21.
61. Gwinnett AJ, Kanca JA 3rd. Micromorphology of the bonded dentin interface and its relationship to bond strength. Am J Dent 1992;5:73–77.
62. Gwinnett AJ. Effect of cavity disinfection on bond strength to dentin. J Esthet Dent 1992;4 Suppl:11–3.
63. Hagger O. Swiss patent 278,946;British patent 687,299. 1951.
64. Han GJ, Kim JH, Chung SN, Chun BH, Kim CK, Seo DG, Son HH, Cho BH. Effects of non-thermal atmospheric pressure pulsed plasma on the adhesion and durability of resin composite to dentin. Eur J Oral Sci 2014;122:417–423.
65. Hanabusa M, Mine A, Kuboki T, Momoi Y, Van Ende A, Van Meerbeek B, De Munck J. Bonding effectiveness of a new 'multi-mode' adhesive to enamel and dentine. J Dent 2012;40:475–484.
66. Hanabusa M, Mine A, Kuboki T, Momoi Y, Van Landuyt KL, Van Meerbeek B, De Munck J. TEM interfacial characterization of an experimental self-adhesive filling material bonded to enamel/dentin. Dent Mater 2011;27:818–824.
67. Hanabusa M, Yoshihara K, Yoshida Y, Okihara T, Yamamoto T, Momoi Y, Van Meerbeek B. Interference of functional monomers with polymerization efficiency of adhesives. Eur J Oral Sci 2016;124:204–209.
68. Hashimoto M, Ito S, Tay FR, Svizero NR, Sano H, Kaga M, Pashley DH. Fluid movement across the resin-dentin interface during and after bonding. J Dent Res 2004;83:843–848.
69. Hass V, Dobrovolski M, Zander-Grande C, Martins GC, Gordillo LA, Rodrigues Accorinte Mde L, Gomes OM, Loguercio AD, Reis A. Correlation between degree of conversion, resin-dentin bond strength and nanoleakage of simplified etch-and-rinse adhesives. Dent Mater 2013;29(9): 921–928.
70. Hass V, Luque-Martinez IV, Gutierrez MF, Moreira CG, Gotti VB, Feitosa VP, Koller G, Otuki MF, Loguercio AD, Reis A. Collagen cross-linkers on dentin bonding: stability of the adhesive interfaces, degree of conversion of the adhesive, cytotoxicity and in situ MMP inhibition. Dent Mater 2016;32:732–741.
71. Heymann HO, Sturdevant JR, Bayne S, Wilder AD, Sluder TB, Brunson WD. Examining tooth flexure effects on cervical restorations: A two-year clinical study. J Am Dent Assoc 1991;122:41–47.
72. Hikita K, Van Meerbeek B, De Munck J, Ikeda T, Van Landuyt K, Maida T, Lambrechts P, Peumans M. Bonding effectiveness of adhesive luting agents to enamel and dentin. Dent Mater 2007;23:71–80.
73. Hiraishi N, Sono R, Sofiqul I, Yiu C, Nakamura H, Otsuki M, Takatsuka T, Tagami J. In vitro evaluation of plant derived agents to preserve dentin collagen. Dent Mater 2013a;29:1048–1054.
74. Hiraishi N, Tochio N, Kigawa T, Otsuki M, Tagami J. Monomer-collagen interactions studied by saturation transfer difference NMR. J Dent Res 2013b;92:284–288.
75. Hoshika S, Kameyama A, Suyama Y, De Munck J, Sano H, Van Meerbeek B. GPDM- and 10-MDP-based self-etch adhesives bonded to burcut and uncut enamel – "Immediate" and "aged" μTBS. J Adhes Dent 2018;20:113–210.
76. Huyck CL. The effect of cetylpyridinium chloride on the bacterial growth in the oral cavity. J Am Pharmaceut Assoc 1945;34(Sci. ed.):5–11.
77. Ikeda T, De Munck J, Shirai K, Hikita K, Inoue S, Sano H, Lambrechts P, Van Meerbeek B. Effect of fracture strength of primer-adhesive mixture on bonding effectiveness. Dent Mater 2005a;21:413–420.
78. Ikeda T, De Munck J, Shirai K, Hikita K, Inoue S, Sano H, Lambrechts P, Van Meerbeek B. Effect of evaporation of primer components on ultimate tensile strengths of primer-adhesive mixture. Dent Mater 2005b; 21: 1051–1058.
79. Imazato S, Kuramoto A, Takahashi Y, Ebisu S, Peters MC. In vitro antibacterial effects of the dentin primer of Clearfil Protect Bond. Dent Mater 2006;22:527–532.

80. Inokoshi S, Hosoda H, Harnirattisai C, Shimada Y. Interfacial structure between dentin and seven dentin bonding systems revealed using argon ion beam etching. Oper Dent 1993;18:8–16.
81. Inoue S, Koshiro K, Yoshida Y, De Munck J, Nagakane K, Suzuki K, Sano H, Van Meerbeek B. Hydrolytic stability of self-etch adhesives bonded to dentin. J Dent Res 2005;84:1160–1164.
82. Inoue S, Van Meerbeek B, Abe Y, Yoshida Y, Lambrechts P, Vanherle G, Sano H. Effect of remaining dentin thickness and the use of conditioner on micro-tensile bond strength of a glass-ionomer adhesive. Dent Mater 2001;17:445–455.
83. Iwaku M, Nakamichi I, Nakamura K, Horie K, Suizu S, Fusayama T. Tags penetrating dentin of a new adhesive resin. Bull Tokyo Med Dent Univ 1981;28:45–51.
84. Kanca J 3rd. Dental adhesion and the All-Bond system. J Esthet Dent 1991;3:129–132.
85. Kanca J 3rd. Resin bonding to wet substrate. 1. Bonding to dentin. Quintessence Int 1992;23:39–41.
86. Kelsey WP 3rd, Latta MA, Vargas MA, Carroll LR, Armstrong SR. Microtensile bond strength of total-etch and self-etch adhesives to the enamel walls of Class V cavities. Am J Dent 2005;18:37–40.
87. Kim YK, Mai S, Mazzoni A, Liu Y, Tezvergil-Mutluay A, Takahashi K, Zhang K, Pashley DH, Tay FR. Biomimetic remineralization as a progressive dehydration mechanism of collagen matrices – implications in the aging of resin-dentin bonds. Acta Biomater 2010;6:3729–3739.
88. Kitagawa H, Takeda K, Kitagawa R, Izutani N, Miki S, Hirose N, Hayashi M, Imazato S. Development of sustained antimicrobial-release systems using poly(2-hydroxyethyl methacrylate)/trimethylolpropane trimethacrylate hydrogels. Acta Biomater 2014;10:4285–4295.
89. Kopperud SE, Tveit AB, Gaarden T, Sandvik L, Espelid I. Longevity of posterior dental restorations and reasons for failure. Eur J Oral Sci 2012;120:539–548.
90. Kramer IRH, McLean JW. Alterations in the staining reaction of dentine resulting from a constituent of a new self-polymerising resin. Br Dent J 1952;93:150–153.
91. Kucukyilmaz E, Savas S. Evaluation of different fissuresealant materials and flowable composites used aspit-and-fissure sealants: a 24-month clinical trial. Pediatr Dent 2015;37:468–473.
92. Lee VA, Karthikeyan R, Rawls HR, Amaechi BT. Anti-cariogenic effect of a cetylpyridinium chloride-containing nanoemulsion. J Dent 2010;38: 742–749.
93. Liu Y, Dusevich V, Wong Y. Proanthocyanidins rapidly stabilize the demineralized dentin layer. J Dent Res 2013;92:746–752.
94. Liu Y, Liu Q, Yu QS, Wang Y. Nonthermal atmospheric plasmas in dental restoration. J Dent Res 2016;95:496–505.
95. Liu Y, Tjäderhane L, Breschi L, Mazzoni A, Li N, Mao J, Pashley DH, Tay FR. Limitations in bonding to dentin and experimental strategies to prevent bond degradation. J Dent Res 2011;90:953–968.
96. Loguercio AD, Reis A. Application of a dental adhesive using the self-etch and etch-and-rinse approaches: an 18-month clinical evaluation. J Am Dent Assoc 2008;139:53–61.
97. Lührs AK, De Munck J, Geurtsen W, Van Meerbeek B. Composite cements benefit from light-curing. Dent Mater 2014a;30:292–301.
98. Lührs AK, Pongprueksa P, De Munck J, Geurtsen W, Van Meerbeek B. Curing mode affects bond strength of adhesively luted composite CAD/CAM restorations to dentin. Dent Mater 2014b;30:281–291.
99. Macedo GV, Yamauchi M, Bedran-Russo AK. Effects of chemical cross-linkers on caries-affected dentin bonding. J Dent Res 2009;88:1096–1100.
100. Magne P. Immediate dentin sealing: a fundamental procedure for indirect bonded restorations. J Esthet Restor Dent 2005;17:144–154.
101. Mahn E, Rousson V, Heintze S. Meta-Analysis of the influence of bonding parameters on the clinical outcome of tooth-colored cervical restorations. J Adhes Dent 2015;17:391–403.
102. Makishi P, André CB, Silva JL, Bacelar-Sá R, Correr-Sobrinho L, Giannini M. Effect of storage time on bond strength performance of multimode adhesives to indirect resin composite and lithium disilicate glass ceramic. Oper Dent 2016;41:541–551.
103. Malacarne J, Carvalho RM, de Goes MF, Svizero N, Pashley DH, Tay FR, Yiu CK, Carrilho MR. Water sorption/solubility of dental adhesive resins. Dent Mater 2006;22:973–980.
104. Matsuo K, Yoshihara K, Nagaoka N, Makita Y, Obika H, Okihara T, Matsukawa A, Yoshida Y, Van Meerbeek B. Rechargeable anti-microbial adhesive formulation containing cetylpyridinium chloride montmorillonite. Acta Biomater 2019;100:388–397.
105. Mazzoni A, Angeloni V, Comba A, Maravic T, Cadenaro M, Tezvergil-Mutluay A, Pashley DH, Tay FR, Breschi L. Cross-linking effect on dentin bond strength and MMPs activity. Dent Mater 2018;34:288–295.
106. Mazzoni A, Angeloni V, Sartori N, Duarte S Jr, Maravic T, Tjäderhane L, Pashley DH, Tay FR, Breschi L. Substantivity of carbodiimide inhibition on dentinal enzyme activity over time. J Dent Res 2017;96:902–908.
107. Mazzoni A, Nascimento FD, Carrilho M, Tersariol I, Papa V, Tjäderhane L, Di Lenarda R, Tay FR, Pashley DH, Breschi L. MMP activity in the hybrid layer detected with in situ zymography. J Dent Res 2012;91:467–472.
108. Mazzoni A, Scaffa P, Carrilho M, Tjäderhane L, Di Lenarda R, Polimeni A, Tezvergil-Mutluay A, Tay FR, Pashley DH, Breschi L. Effects of etch-and-rinse and self-etch adhesives on dentin MMP-2 and MMP-9. J Dent Res 2013;92:82–86.
109. Mazzoni A, Tjäderhane L, Checchi V, Di Lenarda R, Salo T, Tay FR, Pashley DH, Breschi L. Role of dentin MMPs in caries progression and bond stability. J Dent Res 2015;94:241–251.
110. McLean JW. Bonding to enamel and dentin (letter). Quintessence Int 1995;26: 234.
111. McLean JW. The pioneers of enamel and dentin bonding. J Adhes Dent 1999;1:185–187.
112. Miletic V, Pongprueksa P, De Munck J, Brooks NR, Van Meerbeek B. Monomer-to-polymer conversion and micro-tensile bond strength to dentine of experimental and commercial adhesives containing diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide or a camphorquinone/amine photo-initiator system. J Dent 2013;41:918–926.
113. Mine A, De Munck J, Cardoso MV, Van Landuyt KL, Poitevin A, Van Ende A, Matsumoto M, Yoshida Y, Kuboki T, Yatani H, Van Meerbeek B. Dentin-smear remains at self-etch adhesive interface. Dent Mater 2014;30:1147–1153.
114. Mine A, De Munck J, Van Ende A, Poitevin A, Matsumoto M, Yoshida Y, Kuboki T, Van Landuyt KL, Yatani H, Van Meerbeek B. Limited interaction of a self-adhesive flowable composite with dentin/enamel characterized by TEM. Dent Mater 2017;33:209–217.
115. Mine A, De Munck J, Vivan Cardoso M, Van Landuyt KL, Poitevin A, Kuboki T, Yoshida Y, Suzuki K, Van Meerbeek B. Enamel-smear compromises bonding by mild self-etch adhesives. J Dent Res 2010;89: 1505–1509.
116. Misra DN, Bowen RL. Adsorption of N-(2-hydroxy-3-methacryloxypropyl)-N-phenylglycine (NPG-GMA) on cupric ion-enriched hydroxyapatite surface to improve chemical bonding between dental resins and teeth. Biomaterials 1981;2:78–82.
117. Montagner AF, Sarkis-Onofre R, Pereira-Cenci T, Cenci MS. MMP Inhibitors on Dentin Stability: A Systematic Review and Meta-analysis. J Dent Res 2014;93:733–743.
118. Montes MA, de Goes MF, da Cunha MR, Soares AB. A morphological and tensile bond strength evaluation of an unfilled adhesive with low-viscosity composites and a filled adhesive in one and two coats. J Dent 2001;29:435–441.
119. Monticelli F, Osorio R, Mazzitelli C, Ferrari M, Toledano M. Limited decalcification/diffusion of self-adhesive cements into dentin. J Dent Res 2008;87(10):974–979.
120. Moraschini V, Fai CK, Alto RM, Dos Santos GO. Amalgam and resin composite longevity of posterior restorations: a systematic review and meta-analysis. J Dent 2015;43:1043–1050.
121. Moretto S, De Munck J, Wehner M, Freitas P, Van Meerbeek B. Microtensile bond strength to femtosecond laser-irradiated dentin. Abstract presented at the 2012 IADR/LAR General Session at Iguaçu Falls, Brazil, J Dent Res 2012;91(Spec Iss B): 22 (abstract).
122. Moretto SG, Russo EM, Carvalho RC, De Munck J, Van Landuyt K, Peumans M, Van Meerbeek B, Cardoso MV. 3-year clinical effectiveness of one-step adhesives in non-carious cervical lesions. J Dent 2013; 41:675–682.
123. Moszner N, Angermann J, Fischer U, Bock T. Monomers for adhesive polymers, 9 – Synthesis, radical photopolymerization, and properties of (meth)acrylamido dihydrogen phosphates. Macromol Mater Eng 2013;298:454-61.
124. Moszner N, Salz U, Zimmermann J. Chemical aspects of self-etching enamel-dentin adhesives: a systematic review. Dent Mater 2005;21: 895–910.
125. Nagarkar S, Theis-Mahon N, Perdigão J. Universal dental adhesives: Current status, laboratory testing, and clinical performance. J Biomed Mater Res B Appl Biomater 2019;107:2121–2131.
126. Nakabayashi N, Kojima K, Masuhara E. The promotion of adhesion by the infiltration of monomers into tooth substrates. J Biomed Mater Res 1982;16:265–273.
127. Nakabayashi N, Watanabe A. [SEM and TEM observation of dentin surface treated for adhesion]. Tokyo Ika Shika Daigaku Iyo Kizai Kenkyusho Hokoku 1983;17:45-55. [Article in Japanese]

128. Nakabayashi N, Watanabe A. [TEM studies of treated dentin surface. The embedding and adhesion mechanisms]. Tokyo Ika Shika Daigaku Iyo Kizai Kenkyusho Hokoku 1985;1 9:31-8. [Article in Japanese]
129. Nakabayashi N. Adhesive bonding with 4-META. Oper Dent 1992;Suppl 5:125–130.
130. Nakabayashi N. Bonding of restorative materials to dentine: the present status in Japan. Int Dent J 1985;35:145–154.
131. Namba N, Yoshida Y, Nagaoka N, Takashima S, Matsuura-Yoshimoto K, Maeda H, Van Meerbeek B, Suzuki K, Takashiba S. Antibacterial effect of bactericide immobilized in resin matrix. Dent Mater 2009;25: 424–430.
132. Navarra CO, Breschi L, Turco G, Diolosà M, Fontanive L, Manzoli L, Di Lenarda R, Cadenaro M. Degree of conversion of two-step etch-and-rinse adhesives: In situ micro-Raman analysis. J Dent 2012;40(9): 711–717.
133. Nedeljkovic I, De Munck J, Slomka V, Van Meerbeek B, Teughels W, Van Landuyt KL. Lack of buffering by composites promotes shift to more cariogenic bacteria. J Dent Res 2016;95:875–881.
134. Nishitani Y, Yoshiyama M, Wadgaonkar B, Breschi L, Mannello F, Mazzoni A, Carvalho RM, Tjäderhane L, Tay FR, Pashley DH. Activation of gelatinolytic/collagenolytic activity in dentin by self-etching adhesives. Eur J Oral Sci 2006;114:160–166.
135. Opdam NJ, van de Sande FH, Bronkhorst E, Cenci MS, Bottenberg P, Pallesen U, Gaengler P, Lindberg A, Huysmans MC, van Dijken JW. Longevity of posterior composite restorations: a systematic review and meta-analysis. J Dent Res 2014;93:943–949.
136. Parise Gré C, Pedrollo Lise D, Ayres AP, De Munck J, Tezvergil-Mutluay A, Seseogullari-Dirihan R, Lopes GC, Van Landuyt K, Van Meerbeek B. Do collagen cross-linkers improve dentin's bonding receptiveness? Dent Mater 2018;34:1679–689.
137. Pashley DH, Tay FR, Breschi L, Tjäderhane L, Carvalho RM, Carrilho M, Tezvergil-Mutluay A. State of the art etch-and-rinse adhesives. Dent Mater 2011;27:1–16.
138. Pashley DH, Tay FR, Carvalho RM, Rueggeberg FA, Agee KA, Carrilho M, Donnelly A, García-Godoy F. From dry bonding to water-wet bonding to ethanol-wet bonding. A review of the interactions between dentin matrix and solvated resins using a macromodel of the hybrid layer. Am J Dent 2007;20:7–20.
139. Pashley DH, Tay FR. Aggressiveness of contemporary self-etching adhesives. Part II: etching effects on unground enamel. Dent Mater 2001;17:430–444.
140. Pedano MS, Li X, Li S, Sun Z, Cokic SM, Putzeys E, Yoshihara K, Yoshida Y, Chen Z, Van Landuyt K, Van Meerbeek B. Freshly-mixed and setting calcium-silicate cements stimulate human dental pulp cells. Dent Mater 2018;34:797–808.
141. Perdigão J, Ceballos L, Giráldez I, Baracco B, Fuentes MV. Effect of a hydrophobic bonding resin on the 36-month performance of a universal adhesive – a randomized clinical trial. Clin Oral Investig 2019;doi: 10.1007/s00784-019-02940-x.
142. Perdigão J, Lambrechts P, Van Meerbeek B, Braem M, Yildiz E, Yücel T, Vanherle G. The interaction of adhesive systems with human dentin. Am J Dent 1996;9:167–173.
143. Perdigão J, Lambrechts P, Van Meerbeek B, Vanherle G, Lopes AL. Field emission SEM comparison of four postfixation drying techniques for human dentin. J Biomed Mater Res 1995;29:1111–1120.
144. Perdigão J, Loguercio AD. Universal or multi-mode adhesives: Why and How? J Adhes Dent 2014;16:193–194.
145. Perdigão J, Muñoz MA, Sezinando A, Luque-Martinez IV, Staichak R, Reis A, Loguercio AD. Immediate adhesive properties to dentin and enamel of a universal adhesive associated with a hydrophobic resin coat. Oper Dent 2014;39:489–499.
146. Perdigão J, Swift Jr EJ. Universal adhesives. J Esthet Restor Dent 2015;27:331–334.
147. Pereira GD, Paulillo LA, De Goes MF, Dias CT. How wet should dentin be? Comparison of methods to remove excess water during moist bonding. J Adhes Dent 2001;3:257–264.
148. Peumans M, De Munck J, Mine A, Van Meerbeek B. Clinical effectiveness of contemporary adhesives for the restoration of non-carious cervical lesions. A systematic review. Dent Mater 2014;30:1089–1103.
149. Peumans M, De Munck J, Van Landuyt K, Van Meerbeek B. Thirteen-year randomized controlled clinical trial of a two-step self-etch adhesive in non-carious cervical lesions. Dent Mater 2015;31:308–314.
150. Peumans M, De Munck J, Van Landuyt KL, Poitevin A, Lambrechts P, Van Meerbeek B. A 13-year clinical evaluation of two three-step etch-and-rinse adhesives in non-carious class-V lesions. Clin Oral Investig 2012;16:129–137.
151. Peumans M, Heeren A, De Munck J, Van Landuyt KL, Van Meerbeek B. Six-year clinical performance of a 2-step self-etch adhesive in non-carious cervical Lesions. Abstract presented at the 2019 CED-IADR meeting at Madrid, Spain, J Dent Res 2019;98(Spec Iss B): 0036 (abstract).
152. Peumans M, Kanumilli P, De Munck J, Van Landuyt K, Lambrechts P, Van Meerbeek B. Clinical effectiveness of contemporary adhesives: a systematic review of current clinical trials. Dent Mater 2005;21:864–881.
153. Peumans M, Valjakova EB, De Munck J, Mishevska CB, Van Meerbeek B. Bonding Effectiveness of Luting Composites to Different CAD/CAM Materials. J Adhes Dent 2016;18:289–302.
154. Peumans M, Voet M, De Munck J, Van Landuyt K, Van Ende A, Van Meerbeek B. Four-year clinical evaluation of a self-adhesive luting agent for ceramic inlays. Clin Oral Investig 2013;17:739–350.
155. Peumans M, Wouters L, De Munck J, Van Meerbeek B, Van Landuyt K. Nine-year clinical performance of a HEMA-free one-step self-etch adhesive in noncarious cervical lesions. J Adhes Dent 2018;20:195–203.
156. Poitevin A, De Munck J, Van Ende A, Suyama Y, Mine A, Peumans M, Van Meerbeek B. Bonding effectiveness of self-adhesive composites to dentin and enamel. Dent Mater 2013;29:221–230.
157. Politano G, Van Meerbeek B, Peumans M. Nonretentive bonded ceramic partial crowns: Concept and simplified protocol for long-lasting dental restorations. J Adhes Dent 2018;20:495–510.
158. Pongprueksa P, De Munck J, Inokoshi M, Van Meerbeek B. Polymerization efficiency affects interfacial fracture toughness of adhesives. Dent Mater 2018;34(4):684–692.
159. Popkin DL, Zilka S, Dimaano M, Fujioka H, Rackley C, Salata R, Griffith A, Mukherjee PK, Ghannoum MA, Esper F. Cetylpyridinium chloride (CPC) exhibits potent, rapid activity against influenza viruses in vitro and in vivo. Pathog Immun 2017;2:252–269.
160. Pucci CR, Gu LS, Zhang HY, Song Q, Xia VW, Davis LB, de Souza Andrade D, Mazzoni A, Breschi L, Pashley DH, Tay FR, Niu LN. Water-associated attributes in the contemporary dentin bonding milieu. J Dent 2018;74:79–89.
161. Rahimian-Imam S, Ramazani N, Fayazi MR. Marginalmicroleakage of conventional fissure sealants andself-adhering flowable composite as fissure sealant inpermanent teeth. J Dent (Tehran) 2015;12:430–435.
162. Reis A, Albuquerque M, Pegoraro M, Mattei G, Bauer JR, Grande RH, Klein-Junior CA, Baumhardt-Neto R, Loguercio AD. Can the durability of one-step self-etch adhesives be improved by double application or by an extra layer of hydrophobic resin? J Dent 2008;36:309–315.
163. Reis AF, Giannini M, Pereira PN. Influence of water-storage time on the sorption and solubility behavior of current adhesives and primer/adhesive mixtures. Oper Dent 2007;32:53–59.
164. Retief DH, Austin JC, Fatti LP. Pulpal response to phosphoric acid. J Oral Pathol 1974;3:114–122.
165. Ricard-Blum S, Ville G. Collagen cross-linking. Int J Biochem 1989;21: 1185–1189.
166. Roggendorf MJ, Krämer N, Appelt A, Naumann M, Frankenberger R. Marginal quality of flowable 4-mm base vs. conventionally layered resin composite. J Dent 2011;39:643–647.
167. Ruyter IE. The chemistry of adhesive agents. Oper Dent 1992;Suppl 5: 32–43.
168. Sadek FT, Braga RR, Muench A, Liu Y, Pashley DH, Tay FR. Ethanol wet-bonding challenges current anti-degradation strategy. J Dent Res 2010a;89:1499–504.
169. Sadek FT, Castellan CS, Braga RR, Mai S, Tjäderhane L, Pashley DH, Tay FR. One-year stability of resin-dentin bonds created with a hydrophobic ethanol-wet bonding technique. Dent Mater 2010b;26:380–386.
170. Salz U, Zimmermann J, Zeuner F, Moszner N. Hydrolytic stability of self-etching adhesive systems. J Adhes Dent 2005;7:107–116.
171. Sano H, Takatsu T, Ciucchi B, Horner JA, Matthews WG, Pashley DH. Nanoleakage: leakage within the hybrid layer. Oper Dent 1995a;20:18–25.
172. Sano H, Yoshiyama M, Ebisu S, Burrow MF, Takatsu T, Ciucchi B, Carvalho R, Pashley DH. Comparative SEM and TEM observations of nanoleakage within the hybrid layer. Oper Dent 1995b;20:160–167.
173. Sarr M, Mine A, De Munck J, Cardoso MV, Kane AW, Vreven J, Van Meerbeek B, Van Landuyt KL. Immediate bonding effectiveness of contemporary composite cements to dentin. Clin Oral Investig 2010;14: 569–577.
174. Scotti N, Cavalli G, Gagliani M, Breschi L. New adhesives and bonding techniques. Why and when? Int J Esthet Dent 2017;12:524–535.
175. Seseogullari-Dirihan R, Apollonio F, Mazzoni A, Tjaderhane L, Pashley D, Breschi L, Tezvergil-Mutluay A. Use of crosslinkers to inactivate dentin MMPs. Dent Mater 2016 ;32:423–432.

176. Sezinando A, Luque-Martinez I, Muñoz MA, Reis A, Loguercio AD, Perdigão J. Influence of a hydrophobic resin coating on the immediate and 6-month dentin bonding of three universal adhesives. Dent Mater 2015;31:e236–246.
177. Siqueira F, Cardenas AM, Gutierrez MF, Malaquias P, Hass V, Reis A, Loguercio AD, Perdigão J. Laboratory performance of universal adhesive systems for luting CAD/CAM restorative materials. J Adhes Dent 2016;18:331–340.
178. Sorsa T, Tjäderhane L, Salo T. Matrix metalloproteinases (MMPs) in oral diseases. Oral Dis 2004;10:311–318.
179. Sugizaki J. The effect of the various primers on the dentin adhesion of resin composites – SEM and TEM observations of the resin-impregnated layer and adhesion promoting effect of the primers. Jpn J Conserv Dent 1991;34:228–265.
180. Suyama Y, de Munck J, Cardoso MV, Yamada T, Van Meerbeek B. Bond durability of self-adhesive composite cements to dentine. J Dent 2013a;41:908–917.
181. Suyama Y, Lührs AK, De Munck J, Mine A, Poitevin A, Yamada T, Van Meerbeek B, Cardoso MV. Potential smear layer interference with bonding of self-etching adhesives to dentin. J Adhes Dent 2013b;15:317–324.
182. Tay FR, Carvalho R, Sano H, Pashley DH. Effect of smear layers on the bonding of a self-etching primer to dentin. J Adhes Dent 2000;2:99–116.
183. Tay FR, Frankenberger R, Krejci I, Bouillaguet S, Pashley DH, Carvalho RM, Lai CN. Single-bottle adhesives behave as permeable membranes after polymerization. I. In vivo evidence. J Dent 2004;32:611–621.
184. Tay FR, Gwinnett AJ, Pang KM, Wei SH. Resin permeation into acid-conditioned, moist, and dry dentin: a paradigm using water-free adhesive primers. J Dent Res 1996a;75:1034–1044.
185. Tay FR, Gwinnett AJ, Pang KM, Wei SH. Structural evidence of a sealed tissue interface with a total-etch wet-bonding technique in vivo. J Dent Res 1994;73:629–636.
186. Tay FR, Gwinnett JA, Wei SH. Micromorphological spectrum from overdrying to overwetting acid-conditioned dentin in water-free acetone-based, single-bottle primer/adhesives. Dent Mater 1996b;12:236–244.
187. Tay FR, Gwinnett JA, Wei SH. Micromorphological spectrum of acid-conditioned dentin following the application of a water-based adhesive. Dent Mater 1998;14:329–338.
188. Tay FR, Gwinnett JA, Wei SH. The overwet phenomenon in two-component acetone-based primers containing aryl amine and carboxylic acid monomers. Dent Mater 1997;13:118–127.
189. Tay FR, Pashley DH, Mak YF, Carvalho RM, Lai SC, Suh BI. Integrating oxalate desensitizers with total-etch two-step adhesive. J Dent Res 2003a;82:703–707.
190. Tay FR, Pashley DH, Suh BI, Carvalho RM, Itthagarun A. Single-step adhesives are permeable membranes. J Dent 2002;30:371–382.
191. Tay FR, Pashley DH. Biomimetic remineralization of resin-bonded acid-etched dentin. J Dent Res 2009;88:719–724.
192. Tay FR, Pashley DH. Guided tissue remineralisation of partially demineralised human dentine. Biomaterials. 2008;29:1127–1137.
193. Tay FR, Pashley DH. Have dentin adhesives become too hydrophilic? J Can Dent Assoc 2003b;69:726–731.
194. Tay FR, Pashley DH. Resin bonding to cervical sclerotic dentin: a review. J Dent 2004;32:173–196.
195. Tay FR, Pashley DH. Water treeing – a potential mechanism for degradation of dentin adhesives. Am J Dent 2003c;16:6–12.
196. Tay FR, Sano H, Carvalho R, Pashley EL, Pashley DH. An ultrastructural study of the influence of acidity of self-etching primers and smear layer thickness on bonding to intact dentin. J Adhes Dent 2000;2:83–98.
197. Tyas MJ, Burns GA, Byrne PF, Cunningham PJ, Dobson BC, Widdop FT. Clinical evaluation of Scotchbond: three-year results. Aust Dent J 1989;34:277–279.
198. Vallittu PK, Boccaccini AR, Hupa L, Watts DC. Bioactive dental materials – Do they exist and what does bioactivity mean? Dent Mater 2018;34:693–694.
199. van den Breemer C, Özcan M, Cune MS, Ayres AA, Van Meerbeek B, Gresnigt M. Effect of immediate dentin sealing and surface conditioning on the microtensile bond strength of resin-based composite to dentin. Oper Dent 2019;44:E289–E98.
200. van Dijken JW, Pallesen U. Three-year randomized clinical study of a one-step universal adhesive and a two-step self-etch adhesive in class II composite restorations. J Adhes Dent 2017;19:287–294.
201. van Dijken JW. A randomized controlled 5-year prospective study of two HEMA-free adhesives, a 1-step self etching and a 3-step etch-and-rinse, in non-carious cervical lesions. Dent Mater 2013;29:e271–280.
202. van Dijken JW. Durability of three simplified adhesive systems in Class V non-carious cervical dentin lesions. Am J Dent 2004;17:27–32.
203. van Dijken JWV, Pallesen U, Benetti A. A randomized controlled evaluation of posterior resin restorations of an altered resin modified glass-ionomer cement with claimed bioactivity. Dent Mater 2019;35:335–343.
204. Van Landuyt KL, De Munck J, Mine A, Cardoso MV, Peumans M, Van Meerbeek B. Filler debonding & subhybrid-layer failures in self-etch adhesives. J Dent Res 2010;89:1045–1050.
205. Van Landuyt KL, De Munck J, Snauwaert J, Coutinho E, Poitevin A, Yoshida Y, Inoue S, Peumans M, Suzuki K, Lambrechts P, Van Meerbeek B. Monomer-solvent phase separation in one-step self-etch adhesives. J Dent Res 2005;84:183–188.
206. Van Landuyt KL, Mine A, De Munck J, Jaecques S, Peumans M, Lambrechts P, Van Meerbeek B. Are one-step adhesives easier to use and better performing? Multifactorial assessment of contemporary one-step self-etching adhesives. J Adhes Dent 2009;11(3):175–190.
207. Van Landuyt KL, Peumans M, De Munck J, Lambrechts P, Van Meerbeek B. Extension of a one-step self-etch adhesive into a multi-step adhesive. Dent Mater 2006;22:533–544.
208. Van Landuyt KL, Snauwaert J, De Munck J, Coutinho E, Poitevin A, Yoshida Y, Suzuki K, Lambrechts P, Van Meerbeek B. Origin of interfacial droplets with one-step adhesives. J Dent Res 2007a;86:739–744.
209. Van Landuyt KL, Snauwaert J, De Munck J, Peumans M, Yoshida Y, Poitevin A, Coutinho E, Suzuki K, Lambrechts P, Van Meerbeek B. Systematic review of the chemical composition of contemporary dental adhesives. Biomaterials 2007b;28:3757–3785.
210. Van Landuyt KL, Snauwaert J, Peumans M, De Munck J, Lambrechts P, Van Meerbeek B. The role of HEMA in one-step self-etch adhesives. Dent Mater 2008a;24:1412–1419.
211. Van Landuyt KL, Yoshida Y, Hirata I, Snauwaert J, De Munck J, Okazaki M, Suzuki K, Lambrechts P, Van Meerbeek B. Influence of the chemical structure of functional monomers on their adhesive performance. J Dent Res 2008b;87:757–761.
212. Van Meerbeek B, Braem M, Lambrechts P, Vanherle G. Morphological characterization of the interface between resin and sclerotic dentine. J Dent 1994;22:141–146.
213. Van Meerbeek B, Conn LJ Jr, Duke ES, Eick JD, Robinson SJ, Guerrero D. Correlative transmission electron microscopy examination of nondemineralized and demineralized resin-dentin interfaces formed by two dentin adhesive systems. J Dent Res 1996;75:879–888.
214. Van Meerbeek B, De Munck J, Mattar D, Van Landuyt K, Lambrechts P. Microtensile bond strengths of an etch&rinse and self-etch adhesive to enamel and dentin as a function of surface treatment. Oper Dent 2003;28:647–660.
215. Van Meerbeek B, De Munck J, Yoshida Y, Inoue S, Vargas M, Vijay P, Van Landuyt K, Lambrechts P, Vanherle G. Buonocore memorial lecture. Adhesion to enamel and dentin: current status and future challenges. Oper Dent 2003;28:215–235.
216. Van Meerbeek B, Dhem A, Goret-Nicaise M, Braem M, Lambrechts P, Vanherle G. Comparative SEM and TEM examination of the ultrastructure of the resin-dentin interdiffusion zone. J Dent Res 1993;72:495–501.
217. Van Meerbeek B, Eick JD, Robinson SJ. Epoxy-embedded versus non-embedded TEM examination of the resin-dentin interface. J Biomed Mater Res 1997;35:191–197.
218. Van Meerbeek B, Frankenberger R. Editorial: On our way towards self-adhesive restorative materials? J Adhes Dent 2019;21:295–296.
219. Van Meerbeek B, Frankenberger R. Editorial: What's next after "universal" adhesives, "bioactive" adhesives? J Adhes Dent 2017;19:459–460.
220. Van Meerbeek B, Inokoshi S, Braem M, Lambrechts P, Vanherle G. Morphological aspects of the resin-dentin interdiffusion zone with different dentin adhesive systems. J Dent Res 1992a;71:1530–540.
221. Van Meerbeek B, Lambrechts P, Inokoshi S, Braem M, Vanherle G. Factors affecting adhesion to mineralized tissues. Oper Dent 1992b;Suppl 5:111–124.
222. Van Meerbeek B, Peumans M, Poitevin A, Mine A, Van Ende A, Neves A, De Munck J. Relationship between bond-strength tests and clinical outcomes. Dent Mater 2010;26:e100–121.
223. Van Meerbeek B, Peumans M, Verschueren M, Gladys S, Braem M, Lambrechts P, Vanherle G. Clinical status of ten dentin adhesive systems. J Dent Res 1994;73:1690–1702.
224. Van Meerbeek B, Vargas M, Inoue S, Yoshida Y, Perdigão J, Lambrechts P, Vanherle G. Microscopy investigations. Techniques, results, limitations. Am J Dent 2000;13(Spec No):3D-18D.
225. Van Meerbeek B, Willems G, Celis JP, Roos JR, Braem M, Lambrechts P, Vanherle G. Assessment by nano-indentation of the hardness and elasticity of the resin-dentin bonding area. J Dent Res 1993;72:1434–1442.

226. Van Meerbeek B, Yoshida Y, Lambrechts P, Vanherle G, Duke ES, Eick JD, Robinson SJ. A TEM study of two water-based adhesive systems bonded to dry and wet dentin. J Dent Res 1998;77:50–59.
227. Van Meerbeek B, Yoshida Y, Snauwaert J, Hellemans L, Lambrechts P, Vanherle G, Wakasa K, Pashley DH. Hybridization effectiveness of a two-step versus a three-step smear layer removing adhesive system examined correlatively by TEM and AFM. J Adhes Dent 1999;1:7–23.
228. Van Meerbeek B, Yoshihara K, Yoshida Y, Mine A, De Munck J, Van Landuyt KL. State of the art of self-etch adhesives. Dent Mater 2011; 27:17–28.
229. Van Meerbeek B, Yoshihara K. Clinical recipe for durable dental bonding: why and how? J Adhes Dent 2014;16:94.
230. Van Meerbeek B. Dentine adhesion: morphological physico-chemical and clinical aspects. KU Leuven PhD dissertation 1993.
231. Vanherle G, Lambrechts P, Braem M. An evaluation of different adhesive restorations in cervical lesions. J Prosthet Dent 1991;65:341–347.
232. Wang Y, Spencer P. Continuing etching of an all-in-one adhesive in wet dentin tubules. J Dent Res 2005;84:350–354.
233. Wang Z, Shen Y, Haapasalo M. Dental materials with antibiofilm properties. Dent Mater 2014;30:e1–16.
234. Yamaguchi M, Yoshida K, Suzuki R, Nakamura H. Root canal irrigation with citric acid solution. J Endod 1996;22:27–9.
235. Yao C, Yu J, Wang Y, Tang C, Huang C. Acidic pH weakens the bonding effectiveness of silane contained in universal adhesives. Dent Mater 2018;34:809–818.
236. Yao C, Zhou L, Yang H, Wang Y, Sun H, Guo J, Huang C. Effect of silane pretreatment on the immediate bonding of universal adhesives to computer-aided design/computer-aided manufacturing lithium disilicate glass ceramics. Eur J Oral Sci 2017;125:173–180.
237. Yoshida Y, Nagakane K, Fukuda R, Nakayama Y, Okazaki M, Shintani H, Inoue S, Tagawa Y, Suzuki K, De Munck J, Van Meerbeek B. Comparative study on adhesive performance of functional monomers. J Dent Res 2004;83:454–458.
238. Yoshida Y, Van Meerbeek B, Nakayama Y, Snauwaert J, Hellemans L, Lambrechts P, Vanherle G, Wakasa K. Evidence of chemical bonding at biomaterial-hard tissue interfaces. J Dent Res 2000;79:709–714.
239. Yoshida Y, Van Meerbeek B, Nakayama Y, Yoshioka M, Snauwaert J, Abe Y, Lambrechts P, Vanherle G, Okazaki M. Adhesion to and decalcification of hydroxyapatite by carboxylic acids. J Dent Res 2001;80: 1565–1569.
240. Yoshida Y, Yoshihara K, Hayakawa S, Nagaoka N, Okihara T, Matsumoto T, Minagi S, Osaka A, Van Landuyt K, Van Meerbeek B. HEMA inhibits interfacial nano-layering of the functional monomer MDP. J Dent Res 2012;91:1060–1065.
241. Yoshida Y, Yoshihara K, Nagaoka N, Hayakawa S, Torii Y, Ogawa T, Osaka A, Van Meerbeek B. Self-assembled nano-layering at the adhesive interface. J Dent Res 2012;91:376–381.
242. Yoshihara K, Hayakawa S, Nagaoka N, Okihara T, Yoshida Y, Van Meerbeek B. Etching efficacy of self-etching functional monomers. J Dent Res 2018a;97:1010–1016.
243. Yoshihara K, Hayakawa S, Nagaoka N, Yoshida Y, Van Meerbeek B. Chemical interaction of a novel functional monomer with hydroxyapatite/dentin. Abstract presented at the 2017 IADR/AADR/CADR General Session at San Francisco, CA, J Dent Res 2017a;96(Spec Iss A): 1713 (abstract).
244. Yoshihara K, Nagaoka N, Hayakawa S, Okihara T, Yoshida Y, Van Meerbeek B. Chemical interaction of glycero-phosphate dimethacrylate (GPDM) with hydroxyapatite and dentin. Dent Mater 2018b;34:1072–1081.
245. Yoshihara K, Nagaoka N, Maruo Y, Sano H, Yoshida Y, Van Meerbeek B. Bacterial adhesion not inhibited by ion-releasing bioactive glass filler. Dent Mater 2017b;33:723–734.
246. Yoshihara K, Nagaoka N, Okihara T, Kuroboshi M, Hayakawa S, Maruo Y, Nishigawa G, De Munck J, Yoshida Y, Van Meerbeek B. Functional monomer impurity affects adhesive performance. Dent Mater 2015; 31:1493–501.
247. Yoshihara K, Nagaoka N, Sonoda A, Maruo Y, Makita Y, Okihara T, Irie M, Yoshida Y, Van Meerbeek B. Effectiveness and stability of silane coupling agent incorporated in 'universal' adhesives. Dent Mater 2016;32:1218–1225.
248. Yoshihara K, Nagaoka N, Yoshida Y, Van Meerbeek B, Hayakawa S. Atomic level observation and structural analysis of phosphoric-acid ester interaction at dentin. Acta Biomater 2019;97:544–556.
249. Yoshihara K, Yoshida Y, Hayakawa S, Nagaoka N, Irie M, Ogawa T, Van Landuyt KL, Osaka A, Suzuki K, Minagi S, Van Meerbeek B. Nanolayering of phosphoric acid ester monomer on enamel and dentin. Acta Biomater 2011a;7:3187–3195.
250. Yoshihara K, Yoshida Y, Hayakawa S, Nagaoka N, Kamenoue S, Okihara T, Ogawa T, Nakamura M, Osaka A, Van Meerbeek B. Novel fluorocarbon functional monomer for dental bonding. J Dent Res 2014; 93:189–194.
251. Yoshihara K, Yoshida Y, Hayakawa S, Nagaoka N, Torii Y, Osaka A, Suzuki K, Minagi S, Van Meerbeek B, Van Landuyt KL. Self-etch monomer-calcium salt deposition on dentin. J Dent Res 2011b;90:602–606.
252. Yoshihara K, Yoshida Y, Nagaoka N, Fukegawa D, Hayakawa S, Mine A, Nakamura M, Minagi S, Osaka A, Suzuki K, Van Meerbeek B. Nano-controlled molecular interaction at adhesive interfaces for hard tissue reconstruction. Acta Biomater 2010;6:3573–3582.
253. Yoshihara K, Yoshida Y, Nagaoka N, Hayakawa S, Okihara T, De Munck J, Maruo Y, Nishigawa G, Minagi S, Osaka A, Van Meerbeek B. Adhesive interfacial interaction affected by different carbon-chain monomers. Dent Mater 2013;29:888–897.
254. Yoshihara K. Nano-molecular interaction at the adhesive interface with hydroxyapatite and tooth tissue. KU Leuven BIOMAT PhD dissertation 2014.
255. Yoshioka M, Yoshida Y, Inoue S, Lambrechts P, Vanherle G, Nomura Y, Okazaki M, Shintani H, Van Meerbeek B. Adhesion/decalcification mechanisms of acid interactions with human hard tissues. J Biomed Mater Res 2002;59:56–62.
256. Yoshiyama M, Sano H, Ebisu S, Tagami J, Ciucchi B, Carvalho RM, Johnson MH, Pashley DH. Regional strengths of bonding agents to cervical sclerotic root dentin. J Dent Res 1996;75:1404–1413.
257. Zhang K, Zhang N, Weir MD, Reynolds MA, Bai Y, Xu HHK. Bioactive dental composites and bonding agents having remineralizing and antibacterial characteristics. Dent Clin North Am 2017;61:669–687.
258. Zhang Y, Yu Q, Wang Y. Non-thermal atmospheric plasmas in dental restoration: improved resin adhesive penetration. Dent Mater 2012;28: 1232–1239.
259. Zheng P, Zaruba M, Attin T, Wiegand A. Effect of different matrix metalloproteinase inhibitors on microtensile bond strength of an etch-and-rinse and a self-etching adhesive to dentin. Oper Dent 2015;40:80–86.

Clinical relevance: This paper reviewed literature with regard to the current status of dental adhesive technology, providing evidenced-based guidelines to clinically reliably, durably, and predictably bond to tooth enamel and dentin.